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Poster

566. Cytoskeletal Functions in Neurodevelopment

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 566.01/A1

Topic: A.04. Axon and Dendrite Development

Support: NIH Grant R01NS076640

Title: Neuronal polarization and morphogenesis are disrupted by mutation of Kinesin-6 family member Kif20b

Authors: *N. DWYER, T. D. CUPP, T. L. ARNELL, A. SHRESTHA, K. M. JANISCH; Cell Biol, Univ. Virginia, Charlottesvle, VA

Abstract: Neurons must polarize and adopt complex morphologies in order to perform their functions. The mechanisms underlying these processes remain poorly understood. Recent evidence suggests that cytokinesis structures and proteins may be involved in neuronal polarization. A mouse mutant in the cytokinetic kinesin Kif20b may provide insights into mechanisms of neural stem cell division and neuronal morphogenesis, and possible relationships between the two. We previously reported that a loss-of-function mutation in the vertebrate-specific Kinesin-6 gene, *Kif20b*, disrupts growth of the cerebral cortex and causes microcephaly and perinatal lethality. Loss of Kif20b disrupts late cytokinesis (abscission) of cortical neural stem cells, reduces production of progenitors and neurons, and increases apoptosis in the embryonic cortex. The *Kif20b*^{magoo} mutant cortex has thinner neuronal layers, but they are properly ordered. Here we show that the cortical neurons that are produced in the *Kif20b* mutants display robust morphological differences from control neurons in dissociated cultures. Mutant neurons show reduced polarization at both 2 and 4 days *in vitro*. Among mutant neurons that do polarize, their axons have increased branching, their dendrites are longer, and both appear thicker. In addition, growth cone filopodia are longer, while growth cone areas are not different from controls. These morphological differences are not due to fate changes in cell or neuron types. They could arise from abnormalities in the cytokinesis events at the birth of these neurons, and/or from post-division requirements for this kinesin in regulating the neuronal cytoskeleton. We are addressing these possibilities, roles of Kif20b in cytoskeleton regulation, and candidate downstream effectors. We are also testing whether these *in vitro* abnormalities in neuronal polarization and morphogenesis are also found *in vivo* in *Kif20b* mutant mice.

Disclosures: N. Dwyer: None. **T.D. Cupp:** None. **T.L. Arnell:** None. **A. Shrestha:** None. **K.M. Janisch:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 566.02/A2

Topic: A.04. Axon and Dendrite Development

Support: NS044916

NS069688

Title: Spectrin cytoskeleton orchestrates peripheral nervous system node of Ranvier assembly and axon integrity

Authors: *Y. HUANG, C. ZHANG, D. ZOLLINGER, M. RASBAND;
Baylor Col. of Med., Houston, TX

Abstract: Spectrins are a family of cytoskeletal proteins, that provide structural support of the cell membrane, link membrane-associated proteins to actin and serve as platforms for cell signaling. Spectrins consist of α and β subunits, forming heterotetramers to function as a complex. Among the spectrins, αII-spectrin is the only α-spectrin expressed in the nervous system. αII-spectrin is also implicated in neurological disorders, including traumatic brain injury, spinal cord injury, neurodegenerative diseases and West syndrome. Moreover, embryonic lethality of constitutive knockout mice with nervous system malformation highlights the importance of αII-spectrin in the nervous system. To investigate the potential function of αII-spectrin in the brain, we generated αII-spectrin conditional knockout (cko) mice. Using Nestin-cre mice, we generated αII-spectrin cko mice to examine the function of αII-spectrin in the central nervous system (CNS). Mutant animals had profound neurological phenotypes and died perinatally. Loss of αII-spectrin results in dramatic reduction in all brain β-spectrins. To specifically interrogate the spectrin function in neurons and to bypass the perinatal lethality observed in Nestin-cre; αII-spectrin cko mice, we generated sensory neuron specific αII-spectrin cko mice using advillin-cre. Peripheral sensory neuron KO mice had abnormal gait and motor incoordination while nociception remained intact. We found that dorsal root nerve conduction was significantly reduced in cko mice. Immunohistochemistry showed that mutant mice had fewer nodes of Ranvier. Moreover, paranodal junctions, flanking nodes, were extensively disrupted. We also found widespread axon degeneration in advillin-cre cko mice. Consistent with axonal injury, we observed ATF3 in cko dorsal root ganglia (DRG) neurons beginning at P10 and increasing with age. Remarkably, ATF3+ neurons are mostly large diameter neurons; small

TRPV1+ neurons did not have the injury marker. This difference could account for the motor coordination defects caused by deficits in proprioception while nociception remains unaffected.

Disclosures: **Y. Huang:** None. **C. Zhang:** None. **D. Zollinger:** None. **M. Rasband:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

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Program#/Poster#: 566.03/A3

Topic: A.04. Axon and Dendrite Development

Support: NS50356

GM63074

Title: DTPPP, a novel microtubule polymerizing protein, is essential for proper *Drosophila* embryonic CNS organization

Authors: ***R. E. MINO**[1], A. L. RISINGER[2], S. BANERJEE[1], S. L. ROGERS[3], C. ROHENA[2], M. A. BHAT[1];
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Abstract: The cytoskeleton is an essential cellular structure that helps in providing shape, support and movement. In the nervous system, the microtubule cytoskeleton has specific characteristics that allow it to play important roles in the development and function of its constituent cells. Through a genomic deficiency screen, aimed at the identification and characterization of novel molecular players involved in the development of the embryonic *Drosophila* midline, we discovered an uncharacterized cytoskeleton-associated protein which we have named DTPPP (*Drosophila* Tubulin Polymerization-Promoting Protein). DTPPP displays high structural similarity to its mammalian counterpart, Tubulin Polymerization-Promoting Protein (TPPP), suggesting a conserved role across species. TPPP has been implicated in severe pathologies such as Multiple Sclerosis and Parkinson's disease; however, no mutational analysis of the *tppp* locus had been carried out in any species. In *Drosophila*, immunohistochemical analyses indicate that DTPPP is temporally and spatially regulated in the embryonic nervous system. To further understand its role in the development of the embryonic CNS, we generated a *dtppp* null mutation through transposon mobilization strategies. In-depth *in vivo* analyses on *dtppp* null and overexpressing embryos reveal that changes in DTPPP expression result in

neuronal phenotypes, including cell misplacement as well as axon targeting and projection extension defects. Further work uncovered that these developmental defects, observed in the absence or with increased levels of DTPPP, are the result of its effects on microtubules. Biochemical microtubule polymerization assays show that DTPPP can directly interact with purified tubulin to increase microtubule polymerization and bundling. Ongoing studies are aimed at the identification of other DTPPP interacting partners in defining the mechanism of microtubule polymerization in cells. Overall, these studies advance our understanding of the molecular details of DTPPP function during development, and may offer a molecular basis to identify mechanisms involved in precipitating neuronal dysfunction at later developmental stages that may involve cytoskeletal proteins.

Disclosures: R.E. Mino: None. **A.L. Risinger:** None. **S. Banerjee:** None. **S.L. Rogers:** None. **C. Rohena:** None. **M.A. Bhat:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 566.04/A4

Topic: A.04. Axon and Dendrite Development

Title: N-terminal and central domains of APC differentially and cooperatively sculpt optic axon growth cones, arbors and targets *in vivo*

Authors: *T. M. ELUL, G. PENG, J. PINZIOTTO, A. SOHAL;
Touro Univ., Vallejo, CA

Abstract: APC is a target of Wnt ligands that regulates microtubule organization, β-catenin stability and other key cellular activities. Here, we studied how the N-terminal and central domains of APC, that are important for indirect cytoskeletal regulation, and for modulating the stability of β-catenin, cooperatively shape optic axons, their growth cones and their arbors in tectal midbrains of intact, living Xenopus tadpoles. Overexpression of the N-terminal domain of APC caused disorganization of optic axons, whereas overexpression of the central domain of APC both dispersed and disorganized optic axons in the optic tract. APCNTER expressing optic axons also formed growth cones that were abnormally wide with long filopodia while optic axons expressing APCβ-cat developed more elongated growth cones with no filopodia in the dorsal optic tract. At a later stage, APCNTER optic axons elaborated arbors that had longer branches but targeted to the appropriate region of the optic tectum. In contrast, optic axons that expressed the APCβ-cat mutant formed arbors that had fewer branches and were frequently

mistargeted within the tectum *in vivo*. These data suggest that the N-terminal and central domains of APC differentially and cooperatively regulate growth cones, arbors and target locations of optic axons *in vivo*.

Disclosures: **T.M. Elul:** None. **G. Peng:** None. **J. Pinziotto:** None. **A. Sohal:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

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Topic: A.04. Axon and Dendrite Development

Support: Ministry of education, culture, sports, Science and technology, Japan

Title: Collapsin response mediator protein 1 (CRMP1) and CRMP2 mediate Semaphorin3A signaling, but through distinct pathway to regulate dendritic spine maturation and patterning

Authors: *Y. GOSHIMA[1], H. MAKIHARA[2], S. NAKAI[3], N. YAMASHITA[4,6], H. NAKAMURA[5,3], F. TANAKA[5], F. NAKAMURA[3];
[1]Yokohama City Univ. Sch. Med., Yokohama, Japan; [2]Mol. Pharmacol. & Neurobio., Yokohama City Univ. Grad. Sch. of Med., Yokohama, Japan; [3]Mol. Pharmacol. & Neurobio., [4]Departments of Mol. Pharmacol. & Neurobio., [5]Neurol., Yokohama City Univ. Grad. school of Med., Yokohama, Japan; [6]Biol., Johns Hopkins Univ., Baltimore, MD

Abstract: Collapsin response mediator protein2 (CRMP2), originally identified as an intracellular molecule that mediates Semaphorin3A (Sema3A) signaling, has been implicated in a variety of neurological and psychiatric disorders. CRMP2 also plays an important role in axon elongation and neuronal polarization. However, physiological roles of CRMP2 *in vivo* remain unknown. We previously reported that CRMP1, close homologue to CRMP2, is involved in Sema3A-induced spine maturation. To elucidate physiological roles of CRMP2, we generated CRMP2 gene-deficient mice (crmp2-/-) and performed phenotypic analysis. The crmp2-/- mice had no apparent phenotype and demonstrated normal development and survival. We focused on morphological analysis of the layer V pyramidal neurons in the cerebral cortex using the Golgi - impregnation method. The density of dendritic spines was reduced in the cortical layer V pyramidal neurons of crmp2-/- mice as well as crmp1 -/- mice. We next examined phenotype of double heterozygous mice, crmp2 and sema3A (crmp2+/-;sama3A+/-), crmp1 and sema3A (crmp1+/-;sama3A+/-) , and crmp2 and crmp1 (crmp2+/-;crmp1+/-). The dendritic spine density and branching were significantly reduced in crmp2+/-;sema3A+/- mice as well as crmp1+/-

;sema3A+/- mice. These phenotypes had no genetic interaction between crmp1 and crmp2, although crmp2+/-;crmp1+/- mice showed aberrant morphology of basal dendrites that was distinct from that observed in crmp1 -/- or crmp2-/- mice. These findings suggest that both CRMP1 and CRMP2 mediate Sema3A signaling and regulate dendritic spine maturation and patterning, but through distinct signaling pathways *in vivo*.

Disclosures: Y. Goshima: None. **H. Makihara:** None. **S. Nakai:** None. **N. Yamashita:** None. **H. Nakamura:** None. **F. Tanaka:** None. **F. Nakamura:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 566.06/A6

Topic: A.04. Axon and Dendrite Development

Title: RACK1 is necessary for the formation of point contacts and axon growth

Authors: *L. J. KERSHNER[1], K. WELSHHANS[2];
[1]Dept. of Biol. Sci., [2]Dept. of Biol. Sciences, Sch. of Biomed. Sci., Kent State Univ., Kent, OH

Abstract: The formation of appropriate connectivity in the developing nervous system is dependent on the process of local translation. In developing neurons, select mRNAs are transported to and locally translated within growth cones, the pathfinding structures at the tip of extending axons. However, the specific substructural locations in which local translation takes place and the molecular mechanisms underlying this process are not well understood. Local translation of β-actin mRNA within growth cones is necessary for appropriate axon guidance and requires receptor for activated C kinase (RACK1), a ribosomal scaffolding protein. We have previously demonstrated that the local translation of β-actin mRNA is dependent on the phosphorylation of RACK1 and zipcode binding protein 1 (ZBP1), an mRNA binding protein. ZBP1 binds to the 3'UTR of β-actin mRNA, represses its translation, and localizes it to growth cones. RACK1 then binds the ZBP1/β-actin mRNA complex on ribosomes. In response to stimulation with brain-derived neurotrophic factor (BDNF), phosphorylation of RACK1 facilitates both the release of β-actin mRNA from ZBP1 and the translation of β-actin mRNA. Here, we investigate whether local translation occurs at point contacts, adhesion sites important for axonal pathfinding, and examine the role of RACK1 in axon growth and guidance. Interestingly, we have now found that RACK1 is localized to point contacts, which led us to hypothesize that point contacts might be a site of local translation in growth cones. Thus, we examined the location of components of the local translation complex relative to point contacts

under both basal and growth factor stimulated conditions in cortical neurons of embryonic day 17 C57BL/6J mice. β-actin mRNA, RACK1, ZBP1 and ribosomes colocalize with paxillin, a marker of point contacts in growth cones. BDNF stimulation increases the colocalization of β-actin mRNA and RACK1 with paxillin. Additionally, the density of point contacts within growth cones increases following BDNF stimulation in a RACK1 and ZBP1 dependent manner. Finally, RACK1 expression and phosphorylation is required for axonal growth. Taken together, these data suggest that RACK1 expression and phosphorylation is critical to the formation of point contacts, the local translation process, and appropriate neuronal development. Furthermore, these data suggest that point contacts are a strategic location for targeted local translation, and critical signaling centers. This research provides insight into how and where local translation is regulated within growth cones, and thereby leads to appropriate connectivity formation in the developing nervous system.

Disclosures: L.J. Kershner: None. **K. Welshhans:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

Location: Hall A

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Topic: A.04. Axon and Dendrite Development

Support: NNSFC 31271141

NNSFC 31330046

Title: FMRP is involved in the NGF-induced axon elongation by locally regulating Map1b and Calm1 translation

Authors: *L. BAO, B. WANG, L. PAN, M. WEI;
Inst. of Biochem. and Cell Biology, Chinese Acad. of Sci., Shanghai, China

Abstract: Objective Previous studies have shown that FMRP is a repressor of its binding transcripts and their association can be affected by extrinsic signaling. Our previous data showed that FMRP mediated axon delivery of *Map1b* and *Calm1*, we next ask if any signals regulate their association in FMRP granules. Nerve growth factor (NGF) plays a critical role in the axon growth in the development of primary sensory neuron. However, the relationship of FMRP with NGF signaling is not identified. **Methods** Microfluidic cultured E13.5 DRG neurons were sampled to detect axon growth rate, the protein and mRNA level of MAP1B and calmodulin

induced by 100 ng/ml NGF. Immunoblotting and quantitative real-time PCR were used to respectively examine the protein and mRNA level of MAP1B and calmodulin. Co-immunoprecipitation experiment was performed to detect the association of FMRP with *Map1b* and *Calm1* respond to NGF in PC12 cells. Loss of FMRP was achieved by AAV-shFMRP-GFP infection and *Fmr1*^{I304N} mutant mice. **Results** (1) Treatment with 100 ng/ml NGF for 2 h in the axon compartment significantly increased the protein level of MAP1B and calmodulin in axons without affecting that in the cell bodies of microfluidic cultured E13.5 DRG neurons. This increase was blocked by co-treatment in the axon compartment with cycloheximide (CHX), an inhibitor of protein synthesis, or K252a, an antagonist of TrkA receptor. Neutrotrophin-3 (NT-3) was unable to induce axonal translation of MAP1B and calmodulin. (2) *Map1b* and *Calm1* remained unchanged both in the cell bodies and axons after NGF treatment in the axon compartment. (3) In PC12 cells endogenously expressing high level of TrkA receptor and exogenously expressing FMRP-GFP-Flag, the co-immunoprecipitated level of *Map1b* and *Calm1* by Flag antibody was significantly decreased after 100 ng/ml NGF treatment for 2 h, whereas that of *Fmr1* was not changed. (4) In the microfluidic cultured E13.5 DRG neurons infected with AAV-shFMRP-GFP, knockdown of FMRP significantly decreased the axon growth rate induced by 100 ng/ml NGF for 1 h and 24 h. Meanwhile, the NGF-induced local translation of MAP1B and calmodulin in axons was totally abolished in the microfluidic culture of E13.5 DRG neurons infected with AAV-shFMRP-GFP. (5) In presence of 100 ng/ml NGF, the axon elongation was significantly decreased in the cultured P14 DRG neurons of *Fmr1*^{I304N} mice compared with WT mice, whereas overexpression of FMRP-GFP completely rescued this defect in the *Fmr1*^{I304N} mice. **Conclusion** These data suggest that NGF triggers release of *Map1b* and *Calm1* from FMRP granules, leading to the escape of MAP1B and calmodulin from translational inhibition of FMRP.

Disclosures: **L. Bao:** None. **B. Wang:** None. **L. Pan:** None. **M. Wei:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 566.08/A8

Topic: A.04. Axon and Dendrite Development

Support: BT/PR12698/BRB/10/717/2009

Title: Formin-2 in neuronal development

Authors: *K. V. GHATE, A. SAHASRABUDHE, A. JACOB, A. GHOSE;
Indian Inst. of Sci. and Research, Pune, Pune, India

Abstract: Precise functioning of nervous system requires establishment of accurate neuronal connections which is tightly regulated by guidance cues during early embryonic development. The exploring growth cone steers in response to these cues to find its synaptic target. This motility is achieved by cue-dependent remodelling of the underlying cytoskeleton that regulates polarity, protrusion and generation of coordinated traction forces. We have screened actin nucleators in developing chick nervous system and have identified Formin 2 (Fmn-2) as a potential candidate, expression of which coincides with the spinal commissural outgrowth and floor plate crossing. Using cultured primary neurons, we show that depletion of Fmn-2 affects filopodial stability and growth cone morphology. Additionally *in vivo* knockdown of Fmn-2 results in defective midline crossing by the commissural interneurons. Taken together our study identifies Fmn-2 as central regulator of growth cone dynamics central to axonal outgrowth and pathfinding.

Disclosures: **K.V. Ghate:** None. **A. Sahasrabudhe:** None. **A. Jacob:** None. **A. Ghose:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

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Topic: A.04. Axon and Dendrite Development

Support: NIH R01 Grant NS082446 to VC

Title: Ran-dependent control of axon elongation

Authors: *D. M. WATT, V. CAVALLI;
Washington Univ. In St. Louis, Saint Louis, MO

Abstract: Axon growth is a critical feature of both neural development and repair. Microtubule dynamics are essential for axon growth; however the molecular mechanisms governing microtubule dynamics in developing axons are complex and not fully understood. The activity of many cytoskeletal regulatory proteins must be carefully controlled to properly coordinate axon growth. Therefore upstream regulators of cytoskeletal remodeling cascades are particularly important to our understanding of axon growth. The small GTPase Ran, originally characterized as a nucleocytoplasmic trafficking protein, was recently demonstrated to also function in ciliary

transport. Furthermore, Ran function is regulated temporally, acting, for example, as a nucleocytoplasmic transport protein during interphase but as a microtubule regulatory protein during mitosis. Several Ran-dependent cytoskeletal remodelers active during mitotic spindle formation are also known to control axon cytoskeletal dynamics. Since Ran is present in developing and adult axons, we explored the possibility that Ran regulates axon growth by controlling microtubule dynamics. Here we present evidence that neuronal Ran levels are precisely tuned to promote axon growth. Both overexpression and knockdown of Ran dramatically reduces axon elongation of sensory neurons plated on laminin, a permissive substrate. Furthermore, we show that Ran promotes axon growth by controlling cytoskeletal dynamics in filipodia. Interestingly, we found that Ran knockdown in sensory neurons plated on chondroitin sulfate proteoglycan, a substrate that mimics the inhibitory environment of the injured central nervous system, promotes axon elongation, in contrast to its effect on permissive substrates. We also investigated proteins that might modulate Ran function in the axon, focusing particularly on the only known cytoplasmic Ran guanine exchange factor, RanBP10. We demonstrate that RanBP10 is enriched in growing axon tips and interacts with Ran in neurons. RanBP10 knockdown significantly reduces axon elongation, an effect that is rescued by expression of Ran, suggesting that RanBP10 promotes axon elongation in a Ran-dependent manner. These results indicate that Ran is a key player in the modulation of axon elongation and might differentially affect axon growth in the peripheral and central nervous systems.

Disclosures: D.M. Watt: None. **V. Cavalli:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: A.04. Axon and Dendrite Development

Support: NIH R00 MH095768

Title: Microtubule plus-end-binding protein, TACC3, promotes axon outgrowth and guidance *in vivo*

Authors: *L. A. LOWERY, B. ERDOGAN, G. CAMMARATA, M. EVANS;
Boston Col., Chestnut Hill, MA

Abstract: Proper neural connections, essential to nervous system function, depend upon precise navigation by the growth cone during development. A fundamental problem in growth cone

biology is how guidance pathways are integrated to coordinate cytoskeletal dynamics and drive accurate axonal navigation. To address this question, we focus on the plus-ends of microtubules (MTs), which explore the growth cone and play a key role in growth cone steering. MT plus-end dynamics are regulated by a conserved family of proteins called 'plus-end-tracking proteins' (+TIPs). Yet, it is unclear how +TIPs interact with each other and with plus-ends to control MT behavior, and how signaling mechanisms downstream of extracellular cues coordinate +TIPs to guide the growth cone in the right direction. We recently determined that the centrosome adaptor, TACC3, is a MT plus-end tracking protein that promotes MT polymerization and axon outgrowth. We predict that guidance cue regulation of TACC3 function in order to spatially restrict MT polymerization within the growth cone may represent a critical mechanism for directing axon guidance *in vivo*. We have begun to test this hypothesis using a combination of high-resolution live imaging of Xenopus laevis axons *in vivo* and *ex vivo*. By examining spinal cord at high resolution, we demonstrate that TACC3-depleted motor neurons and commissural neurons exhibit defects in normal axon outgrowth. We also performed *in vitro* guidance assays and investigated the TACC3-manipulated spinal cord neurons' pathfinding behavior in response to ephrin-A repellent guidance cues. We found that axons overexpressing TACC3 showed less avoidance to ephrin-A repellent signals. Together, our findings reveal that TACC3 functions as an axon outgrowth promoting factor *in vivo* in embryonic spinal cord neurons and in proper axonal navigation during neuronal development.

Disclosures: L.A. Lowery: None. **B. Erdogan:** None. **G. Cammarata:** None. **M. Evans:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

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Program#/Poster#: 566.11/A11

Topic: A.04. Axon and Dendrite Development

Support: NIH Grant NS14428

Title: The role of tau phosphorylation and its 3R and 4R isoforms in regulating microtubule dynamics in living cortical growth cones

Authors: *S. BISWAS, L. GORAL, Q. GAN, K. KALIL;
Dept. of Neurosci., Univ. of Wisconsin, Madison, WI

Abstract: Tau is a phosphorylated microtubule associated protein (MAP) that binds to microtubules (MTs) and regulates their dynamics, essential for growth cone function. The role of tau and its phosphorylation in regulating MT dynamics has been little studied in living neurons. To explore how modifying tau phosphorylation can affect MT dynamics in hamster cortical growth cones, we constructed mutations of the entire tau microtubule- binding domain (MBD) and each of the four repeat regions within the MBD. We first transfected a mutant tau in which Ser262 was changed to non-phosphorylatable Ser262Ala. Although previous work has shown that in cell-free systems this mutated tau prevents tau binding to MTs, our results in HEK cells revealed no changes in tau binding to MTs, suggesting that in a complex cellular environment, mutations at several tau phosphorylation sites may be required to affect tau MT binding. Next, we investigated how each of the Tau phospho mutants affects MT polymerization in growing cortical axons. We transfected hamster cortical neurons with GFP labeled human tau constructs along with the +TIP protein EB3 tagged with td Tomato to label the dynamic plus ends of MTs. Using live cell imaging with TIRF microscopy, we measured the velocities of EB3 comets to determine rates of MT polymerization in growing cortical axons and growth cones. Comparisons among neurons overexpressing full length human tau, vs phospho-mimetic 262D or phospho-deficient S262A human Tau suggested that expression of mutant tau in cortical neurons decreased EB3 comet velocities. To detect effects of different phospho mutants of human tau on MT polymerization, we are knocking down endogenous hamster tau. Different isoforms of human tau are differentially expressed in the developing and mature CNS. In humans and rodent species only the 3R tau isoform, which has three MT-binding sequences is expressed in early development but later in development 4R isoforms, which has four MT-binding repeat sequences, become dominant. However, the functional significance of expression of different tau isoforms during development is not well understood. To determine possible differential effects of the shortest (3RS) and the longest tau isoform (4RL) on MT polymerization, we expressed human GFP-3RS or human GFP-4RL isoforms in hamster cortical neurons. We are co-transfecting with EB3-tdT to compare rates of MT polymerization in growth cones of neurons transfected with different tau isoforms. Our preliminary results suggest that the ability of tau to regulate MT polymerization is dependent not only on its phosphorylation states but also on the specific tau isoform.

Disclosures: **S. Biswas:** None. **L. Goral:** None. **Q. Gan:** None. **K. Kalil:** None.

Poster

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Topic: A.04. Axon and Dendrite Development

Support: R15 HD-080512

Title: Dissociation of netrin-1 receptor UNC5C with TUBB3 is involved in netrin-1-mediated axonal repulsion

Authors: *Q. SHAO, G. LIU;
Biol. Sci., Univ. of Toledo, Toledo, OH

Abstract: The modulation of MT (Microtubule) dynamics is a key event of cytoskeleton remodeling in the growth cone during axon pathfinding. Our previous study has shown that direct interaction of TUBB3, a neuron-specific MT subunit, with DCC (Deleted in Colorectal Cancer) is required for netrin-1-mediated axonal attraction. Here, we propose that the dissociation of polymerized TUBB3 with netrin-1 repulsive receptor UNC5C is involved in netrin-1-mediated axonal repulsion. TUBB3 directly binds to UNC5C and colocalizes with UNC5C in the peripheral area of the axon growth cone. Interestingly, netrin-1 reduces the interaction and the colocalization of TUBB3 and UNC5C. Results from the *in vitro* co-sedimentation assay indicated that the netrin-1 induces dissociation of polymerized TUBB3 with UNC5C. Knockdown of either TUBB3 or UNC5C results in neuronal axon turning defects *in vitro* and misguidance of the DRG (Dorsal root ganglion) axon projection into the spinal cord *in vivo*. These results suggest that the disengagement of netrin-1 receptor UNC5C with polymerized TUBB3 may play an essential role in netrin-1-mediated axon repulsion.

Disclosures: Q. Shao: None. **G. Liu:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

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Program#/Poster#: 566.13/A13

Topic: A.04. Axon and Dendrite Development

Support: Center for Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB)

Title: Subcortical cytoskeleton periodicity in the nervous system

Authors: E. D'ESTE, *D. KAMIN, F. GÖTTFERT, S. W. HELL;
Max Planck Inst. for Biophysical Chem., Göttingen, Germany

Abstract: Recently, far-field optical nanoscopy revealed a periodic cytoskeleton lattice underneath the membrane of axons in fixed hippocampal neurons consisting of actin and spectrin (Xu et al., Science 2013). This lattice has a periodicity of ~190 nm and consists of parallel actin rings spaced apart with spectrin tetramers. By combining live-cell stimulated emission depletion (STED) nanoscopy and the fluorescent probe SiR-Actin, we show that a periodic subcortical actin structure is in fact present in both axons and a subset of dendrites (D'Este et al., Cell Rep. 2015). Beside actin-binding proteins, the periodic arrangement of the subcortical cytoskeleton involves also cell adhesion proteins. For instance, nrCAM and neurofascin are enriched in the axon initial segment (AIS) and they both intercalate with the actin lattice. The periodicity of the subcortical cytoskeleton may be therefore transferred to the extracellular matrix through these adhesion molecules. So far the subcortical cytoskeletal periodicity was proven in unmyelinated cultured hippocampal neurons. In myelinated cells, nodes of Ranvier and AIS share a similar molecular composition. We found the cytoskeletal periodicity also at nodes of Ranvier of mouse sciatic nerve fibers belonging to the peripheral nervous system. In conclusion, we demonstrate that the periodic organization of the subcortical cytoskeleton is in reality not a unique feature of axons of hippocampal neurons, but it is a more general feature of the nervous system.

Disclosures: **E. D'Este:** None. **D. Kamin:** None. **F. Göttfert:** None. **S.W. Hell:** None.

Poster

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Topic: A.04. Axon and Dendrite Development

Support: NIH R01NS042228

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Title: Calsyntenin-1, a kinesin adaptor, regulates microtubule polarity and dynamics during sensory axon arbor development

Authors: ***T. J. LEE**[1], K. ELICEIRI[2], M. HALLORAN[3];
[1]Neurosci. Training Program, [2]LOCI, [3]Departments of Zoology and Neurosci., Univ. of Wisconsin, Madison, WI

Abstract: Axon growth and branching, as well as motor driven axonal transport, are critically dependent on proper organization and dynamics of the microtubule (MT) cytoskeleton. MTs

must organize with correct polarity for delivery of diverse cargos to appropriate subcellular locations, yet the molecular mechanisms regulating MT polarity remain poorly understood. Moreover, how an actively branching axon organizes MT polarity at branch points is unknown. Here we show that Calsyntenin-1 (Clstn-1), a kinesin adaptor required for sensory axon branching, is a crucial regulator of MT polarity and dynamics in developing vertebrate sensory axon arbors. We use high-speed, *in vivo* imaging of polymerizing MT plus-tips to characterize MT dynamics as sensory axon arbors develop in zebrafish. In wildtype embryos the vast majority of MTs are directed in the correct plus-end-distal orientation from early stages of development. Knockdown of Clstn-1 causes an increase in retrograde MT growth. Moreover, these aberrant retrograde MTs most often originate near branch points, suggesting Clstn-1 organizes MT polarity at branch points. Additionally, Clstn-1 knockdown causes both anterograde and retrograde MTs to polymerize for shorter times and distances, implying a role for Clstn-1 in maintaining MT stability. Furthermore, we found that loss of Clstn-1 caused reduced rates of MT polymerization. Together, our results suggest that Clstn-1, in addition to regulating kinesin-mediated cargo transport, also organizes the underlying MT highway during axon arbor development. We are currently investigating potential mechanisms of how Clstn-1 regulates MTs during development by targeting its potential cargos.

Disclosures: **T.J. Lee:** None. **K. Eliceiri:** None. **M. Halloran:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 566.15/A15

Topic: A.04. Axon and Dendrite Development

Support: NICHD 5R00HD058044-05

Title: The development of the corpus callosum is dependent on fibroblast growth factor 8 signaling

Authors: ***C. E. STEWART**, W. C. J. CHUNG;
Biol. Sci., Kent State Univ., Kent, OH

Abstract: Agenesis of the corpus callosum (ACC) is one of the more common clinical brain malformations found in patients with mental retardation, seizures, visual problems, and in more severe cases, holoprosencephaly. Yet, there is still little known about the underlying cause of ACC in these patients. Here, we explored whether fibroblast growth factor (FGF) signaling plays

a role in the development of the corpus callosum. Specifically, FGF8 has been shown to be especially important for normal embryonic development of the corpus callosum. Indeed, *Fgf8* hypomorphic mice not only exhibited severe morphological defects in developing neocortical-related structures, such as cortical thinning, but also ACC. Previously, we presented data showing that ACC in newborn homozygous ($^{neo/neo}$) *Fgf8* hypomorphic mice coincided with a major reduction in the anterior brain midline glial fibrillary acidic protein (GFAP)-expressing astrocytes. A similar, but smaller reduction in GFAP+ astrocytes was also detected in the anterior brain midline region of newborn heterozygous ($^{+/neo}$) mice. In our current studies, we found that these genotype-dependent differences in GFAP astrocytes did not persist into adulthood. Furthermore, using Sholl analysis we showed that the arborization complexity of these astrocytes did not differ between adult wildtype (WT) and heterozygous ($^{+/neo}$) hypomorphic mice. In a subsequent, anatomical study we used neuropilin (NP)-1 immunocytochemistry to examine the morphological organization of the corpus callosum in newborn *Fgf8* hypomorphic mice. These studies showed that NP1-immunoreactive (IR) fibers were dramatically reduced in the newborn indusium griseum, dorsal aspect of the corpus callosum, and midline zipper of $Fgf8^{+/neo}$ and $Fgf8^{neo/neo}$ hypomorphic mice when compared to their WT litter mates. These results suggest that a deficit in FGF8 signaling does not eliminate anterior brain midline astrocytes, but rather delays their maturation (i.e., GFAP expression) until a later postnatal time point. Furthermore, the dramatic genotype-dependent reduction in NP-1-IR fibers suggests that the *Fgf8* hypomorphy also affects the development of the callosal projecting neurons in the neocortical regions.

Disclosures: C.E. Stewart: None. **W.C.J. Chung:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

Location: Hall A

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Program#/Poster#: 566.16/A16

Topic: A.04. Axon and Dendrite Development

Support: NIH NIGMS P01 (GM078195)

RGPIN 249962

RGPIN 402733

CFI #29066

CIHR CGS-M

OGS-PhD

OGS-MSc

Title: The role of Transient Receptor Potential Melastatin 7 (TRPM7) channels in neuronal development under normal and hypoxia-induced stress conditions

Authors: *E. TURLOVA[1], C. BAE[1], M. DEURLOO[1], W. CHEN[1], A. BARSZCZYK[1], D. HORGEN[2], A. FLEIG[3], Z.-P. FENG[1], H.-S. SUN[1];
[1]Univ. of Toronto, Toronto, ON, Canada; [2]Hawaii Pacific Univ., Kaneohe, HI; [3]Queen's Med. Ctr., Honolulu, HI

Abstract: Transient Receptor Potential Melastatin 7 (TRPM7) is a calcium-permeable, non-selective cation channel that has been implicated in biological processes such as cell adhesion, migration, cytoskeleton regulation and survival. As these processes are necessary for neurite outgrowth during neuronal development, we investigated whether TRPM7 is involved in regulation of neurite outgrowth. In this study we demonstrate that TRPM7 is highly expressed in the growth cones of mouse cultured hippocampal neurons, and that both viral knockdown and pharmacological inhibition of TRPM7 preferentially enhanced axonal outgrowth of hippocampal neurons at multiple time points during development. We also showed that pharmacological inhibition of TRPM7 accelerated the progression of neurons into a higher developmental stage, as was evident by the formation of morphologically distinct axons and dendrites. Moreover, we found that TRPM7 co-immunoprecipitated and co-localized with F-actin and α-actinin-1, two major cytoskeletal proteins involved in actin-based growth cone protrusion. Based on these findings we proposed a model of TRPM7-mediated calcium-dependent cytoskeletal dynamics at the neuronal growth cone. We also showed the involvement of TRPM7 in axonal outgrowth under the conditions of hypoxic stress and in neuroprotection against hypoxic-ischemic neuronal injury in the developing brain. Our findings highlight the importance of TRPM7 during neuronal development and suggest a therapeutic potential of TRPM7 blockers in neurodegenerative and neurodevelopmental disease.

Disclosures: **E. Turlova:** None. **C. Bae:** None. **M. Deurloo:** None. **W. Chen:** None. **A. Barszczyk:** None. **D. Horgen:** None. **A. Fleig:** None. **Z. Feng:** None. **H. Sun:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 566.17/A17

Topic: A.04. Axon and Dendrite Development

Support: ProRetina e.V.

Title: Activity-dependent regulation of the cisternal organelle in the axon initial segment during murine visual system development

Authors: *A. SCHLUETER[1], S. ROSSBERGER[2], C. SCHULTZ[3], M. ENGELHARDT[3]; [1]CBTM, Inst. of Neuroanatomy, Heidelberg University, Med. Fac. Mannheim, Mannheim, Germany; [2]Kirchhoff-Institute for Physics, Heidelberg, Germany; [3]Inst. of Neuroanatomy, Med. Fac. Mannheim, Heidelberg, Germany

Abstract: The cisternal organelle (CO) is a calcium storing compartment localized in the axon initial segment (AIS) of cortical principal and hippocampal neurons. The CO shows structural and functional similarities to the spine apparatus in dendritic spines. Both spine apparatus and CO formation are dependent on the expression of the actin-associated protein synaptopodin (synpo). The CO is composed of stacked smooth endoplasmic reticulum and interdigitating plates of electron dense material. It might play a functional role in the temporal and spatial regulation of calcium currents in the AIS and therefore in the generation and timing of action potentials. So far, it is unknown whether synpo/CO expression is activity-regulated during brain development. Moreover, the effect of CO presence and absence on AIS morphological and functional maturation has not been investigated. Here, we examined the impact of synpo expression on the morphological maturation of AIS during murine visual system development and whether morphological maturation of COs occurs in an activity-dependent manner. AIS were investigated in synpo knockout (KO) mice and a subset of synpo-expressing AIS were analyzed in wildtype mice, respectively. Visual deprivation was utilized to study the effect of altered visual input on CO expression and AIS maturation. Dark rearing of mice for 28 and 35 days resulted in significant increases of cluster sizes of synpo in AIS and in length of synpo-bearing AIS in the visual cortex. Interestingly, these light-regulated modifications are irreversible after mice reach postnatal day (P) 28 since light exposure of P28 dark-reared mice for further 7 days did not revoke synpo cluster size elongation and AIS lengthening. In addition, AIS length maturation during visual cortex development is affected by synpo expression. A recently described tri-phasic length maturation is hindered by both, synpo presence or absence. Strikingly, in synpo KO mice visual deprivation leads to AIS length shortening. Taken together, these findings indicate that morphological maturation of COs is subject to activity-dependent dynamic regulation and that CO presence shapes AIS morphological maturation in a subset of visual cortex neurons during visual system development.

Disclosures: **A. Schlueter:** None. **S. Rossberger:** None. **C. Schultz:** None. **M. Engelhardt:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

Location: Hall A

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Program#/Poster#: 566.18/A18

Topic: A.04. Axon and Dendrite Development

Support: P01 ES002848, Project 3

O-3511-2010

Hawaii Residency Programs

Title: Period of axonal exuberance of corpus callosum in rat extends into the first two postnatal weeks

Authors: *M. CULJAT[1,2,3], J. M. JURASKA[2];
[1]Pediatrics, Hawaii Residency Programs, Honolulu, HI; [2]Dept. of Psychology and Program in Neurosci., Univ. of Illinois, Champaign, Urbana/Champaign, IL; [3]Sch. of medicine, Croatian Inst. for Brain Res., Univ. of Zagreb, Zagreb, Croatia

Abstract: INTRODUCTION: Fiber tracts of the mammalian central nervous system undergo axonal overproduction in the perinatal period, followed by a dramatic level of axonal pruning. This has been described in the corpus callosum (CC) in cats (Koppel, Innocenti , 1983) and rhesus monkeys (LaMantia , Rakic, 1990). In rats, pruning has been demonstrated after postnatal days (P) 15 (Kim, Juraska, 1997), but earlier ages are unexplored. MATERIALS AND METHODS: Thirty five Wistar albino rats were perfused at P0, 3, 5, 7, 12, 21 and adult. Midsagittal CC area and length were measured. Additionally, CC at ages P0, P7 and P12 were processed for electron microscopy, and were used for axon and growth cone counts. RESULTS: There is a 1.4x increase of CC midsagittal area between P0 and P3, followed by a plateau between P3 and 21. The midsagittal CC length showed a continuous increase of 1.9x from P0 to P12, followed by a plateau between P12 and P21. The total number of axons linearly increases between P0, P7 and P12 (4.9, 7.9 and 10.8 million, respectively). In all ages analyzed, the dorsal aspect of CC had the highest density. There was no statistical difference in the density of axonal elements between P0 and P7. The CC at P12 had the highest density. The ratio of growth cones to axons significantly increased between P0 and P7, and decreased between P7 and P12 (8.2%, 10% and 5.7%, respectively). CONCLUSIONS: Overproduction of axons in rat CC extends into the first two postnatal weeks. There is continuous increase of CC length during the initial plateau in surface. This coupled with a high ratio of growth cones and increasing density of callosal elements, indicates a high level of internal structural reorganization. Studies of cortical origins of callosal axons in rat showed there is a change in distribution of their neuronal bodies between

P0-P4 and P15 (Olavarria et al. 1984, Ivy et al. 1984), which fits with our interpretation of the callosal changes noted in this study. The higher ratio of growth cones at P7 might indicate an existence of a growth front, supporting the idea of growth in waves of callosal axons instead of continuous growth.

Disclosures: **M. Culjat:** A. Employment/Salary (full or part-time):; Hawaii Residency Programs. **J.M. Juraska:** A. Employment/Salary (full or part-time):; University of Illinois, Champaign.

Poster

566. Cytoskeletal Functions in Neurodevelopment

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 566.19/A19

Topic: A.04. Axon and Dendrite Development

Support: SFARI

Title: Gtf2i regulates neuronal maturation and cognition

Authors: ***M. DEURLOO-STMICHAEL**[1], W. CHEN[1], M. YANG[2], Y. LIN[1], E. TAM[1], M. WU[1], F. LEWIS[2], G. FOLEY[2], J. CRAWLEY[2], H.-S. SUN[1], L. OSBORNE[1], Z.-P. FENG[1]; [1]Univ. of Toronto, Toronto, ON, Canada; [2]MIND institute, Sacramento, CA

Abstract: General Transcription Factor 2I (Gtf2i) has been implicated in the neurodevelopmental phenotypes associated with deletion (Williams syndrome) and duplication (7q11.23 duplication syndrome) of chromosome 7q11.23, primarily in its role as a transcription factor. Here, we show that copy number alterations in Gtf2i have reciprocal effects on cortical neuron maturation. Alteration of Gtf2i copy number in mice regulated axonal outgrowth and branching, and muscarinic M1 receptor-activated calcium signals. Mice with duplication of Gtf2i also show deficits in novel object recognition, in the absence of problems with hippocampal dependent learning and memory. Together, our results provide the first functional insight into the cellular mechanisms that underlie the 7q11.23 disorders.

Disclosures: **M. Deurloo-Stmichael:** None. **W. Chen:** None. **M. Yang:** None. **Y. Lin:** None. **E. Tam:** None. **M. Wu:** None. **F. Lewis:** None. **G. Foley:** None. **J. Crawley:** None. **H. Sun:** None. **L. Osborne:** None. **Z. Feng:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

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Program#/Poster#: 566.20/A20

Topic: A.04. Axon and Dendrite Development

Support: BCCN II A2 01GQ1005A

CNMPB A1-A6

Title: Structural changes of the axon initial segment in neurons derived from spectrin mutant qv3J

Authors: *M. DANNEMEYER[1], E. LAZAROV[2], F. WOLF[3], J. ENDERLEIN[1], A. NEEF[3]; [1]Georg August Univ. Goettingen, Goettingen, Germany; [2]Koret Sch. of Vet. Med., Hebrew Univ. Jerusalem, Israel, Goettingen, Germany; [3]Bernstein Ctr. for Computional Neurosci., MPI for Dynamics and Self-Organization, Goettingen, Germany

Abstract: The distribution and density of neuronal voltage-gated sodium channels (VGSC) is important for neuronal excitability, development and plasticity. High density of VGSCs at the axon initial segment (AIS) depends on the cytoskeletal proteins βIV-spectrin and ankyrin-G (ankG). The mouse mutant *qv^{3J}* has a mutation close to the C-terminus of βIV-spectrin sequence, which shifts the reading frame. [01] We studied the influence on the distribution of βII-spectrin, βIV-spectrin, ankG and VGSCs at the AIS. Neuronal cultures were prepared from hippocampus and immuno-fluorescence was imaged between *7* and *21 days in vitro* with conventional wide-field and stochastic optical reconstruction microscopy (STORM). [02] In wildtype βII- and βIV-spectrin are arranged in the AIS on a very regular structure already at *DIV 7*. During development βII-spectrin density decreases slightly, while the density of βIV-spectrin, ankG and VGSCs increases in the AIS. AnkG is periodically, whereas VGSCs-staining appears semi-periodic. At *DIV 7* wildtype and mutant neurons are very similar with respect to density and periodicity of ankG, VGSCs and βII-spectrin. However, only very little βIV-spectrin is observed in mutant *qv^{3J}* at *DIV 7* and it is completely lost at *DIV 14*. The density and regularity of βII-spectrin is not influenced. In contrast to the development in wildtype almost no increase in ankG and VGSCs is observed in *qv^{3J}*. The ankG which is still present is arranged periodically. The VGSC density in mutant *qv^{3J}* decreases strongly and progressively in the few neurons, that still show a comparably high staining intensity, some periodicity can still be observed. We conclude that βIV-spectrin is incorporated in the existing βII-spectrin grid. The ring-like organization of proteins along the AIS does not depend on βIV-spectrin. The C-terminal mutation *qv^{3J}* causes a complete loss of βIV-spectrin, but some ankG and VGSCs are retained. Remaining ankG is periodic. The remaining VGSCs are so sparse that it is not clear whether they are positioned in

the regular grid. References: [01] Nicholas J Parkinson, Christine L Olsson, Janice L Hallows, Jennifer McKee- Johnson, Bart P Keogh, Konrad Noben-Trauth, Sharon G Kujawa, Bruce L Tempel, "Mutant β-spectrin 4 causes auditory and motor neuropathies in quivering mice" *Nature genetics* (2001) 29(1), 61_65. [02] Ke Xu, Guisheng Zhong, Xiaowei Zhuang, "Actin, spectrin, and associated proteins form a periodic cytoskeletal structure in axons" *Science* (2013) 339(6118), 452-456

Disclosures: M. Dannemeyer: None. **E. Lazarov:** None. **F. Wolf:** None. **J. Enderlein:** None. **A. Neef:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 566.21/A21

Topic: A.04. Axon and Dendrite Development

Support: NIH Grant NS062047

Title: Map7 regulates the development of sensory axon collateral branches via its microtubule bundling activity

Authors: S. TYMANSKYJ[1], *L. MA[2];
[1]Neurosci., Thomas Jefferson Univ., Philadelphia, PA; [2]Neurosci., Dept. of Neurosci., Philadelphia, PA

Abstract: During spinal cord development, sensory neurons in the dorsal root ganglion (DRG) extend both peripheral and central axons which allow connectivity of multiple targets. Centrally, axons form collateral branches, which originate from the axonal shaft, to generate local reflexes. Collateral branch formation is in part regulated by microtubule dynamics and transport, however the precise mechanism microtubules contribute to branching is not clear. Microtubules are known to be regulated by several microtubule associated proteins (MAPs), and here we report a novel function of MAP7, a lesser known MAP previously identified in *Drosophila*. MAP7 has been linked to kinesin functions, but its function in neurons has not been established. We report a novel function of MAP7 in collateral development of DRG sensory neurons. MAP7 expression in DRGs starts at the time of collateral formation. Precocious over-expression or knockdown of MAP7 in culture leads to effects consistent with its branching function during DRG development. This function is mediated primarily by the amino-terminal microtubule binding domain and the central phosphorylation domain, which together create stable, long and curly

microtubule bundles. Time-lapse imaging shows that the bundling activity enters nascent branches and accumulates in the base after branch initiation, suggesting a role in branch maturation. Furthermore, both microtubule bundling and axon branching can be regulated by phosphorylation at a specific site. Finally, the mshi mouse expressing a truncated form of MAP7 has excessive collateral invasion into the spinal cord. Overall we have identified a novel intrinsic mechanism regulating axon collateral development by MAP7. This mechanism is mediated by the ability of MAP7 to bundle microtubules that lead to the stabilization of newly formed collaterals.

Disclosures: **S. Tymanskyj:** None. **L. Ma:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

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Topic: A.04. Axon and Dendrite Development

Support: TWU Department of Biology

TWU Undergraduate Microgrant Program

TWU Reseach Enhancement Program

Title: Identifying signaling cascades involved in growth and cell clustering of functional, non-prenylatable RhoA and Rac1

Authors: ***N. G. RAUT**, J. M. REDDY, K. RODEN, D. L. HYNDS;
Biol., Texas Women's Univ., Denton, TX

Abstract: The Rho guanine triphosphatase (GTPase) are highly characterized and GTPase proteins that act as molecular switches operating between an active GTP-bound state and an inactive GDP-bound state. These proteins play a pivotal role in neuronal differentiation and affect neurite outgrowth, axonal guidance, cell migration, cytokinesis and endocytosis. RhoA promotes assembly of focal adhesion complexes and formation of stress fibers. RhoA regulates the organization of actin cytoskeleton and several other cellular functions in response to the extracellular signals. On the other hand, Rac1 stimulates assembly of multimolecular focal complexes at plasma membrane, induces the peripheral actin accumulations, regulates membrane protrusions, membrane ruffling and formation of lamellipodia and filopodia. The interaction between RhoA and Rac1 is not well explored, though they are thought to be antagonist to each

other. Both require prenylation for membrane localization, though active forms of both have been found in other cellular compartments (GTP-bound Rac1 in the cytosol and GTP-RhoA primarily in the cytosol and nucleus). We designed non-prenylatable Rac1 and RhoA constructs to test how inhibiting prenylation affects morphology and the location of active RhoA and Rac1. Western blot analysis suggested that an increase in ARP2/3-WAVE complexing led to the increase in cell clustering after transfection of the non-prenylatable Rac1 construct and decrease in the prenylatable RhoA construct. An increase in cofilin was observed in after transfection with the wild-type RhoA construct leading to neurite outgrowth and ERK and JNK phosphorylation was increased when cells were transfected with non-prenylatable RhoA or Rac1. We have found transfection of these constructs in rat cortical neurons increase neurite outgrowth (for non-prenylatable RhoA) and neurite formation (for non-prenylatable Rac1). Both retained the ability to be made active independent of membrane targeting by prenylation. With emerging evidence of differential activation of these Rho GTPases based on their subcellular localization, elucidating the signaling cascades of the active GTPases may identify novel targets to facilitate axon regeneration in traumatic or degenerative neurological conditions. This research was supported by the TWU Department of Biology, Undergraduate Microgrant programs . We would like to thank Dr. DiAnna Hynds and laboratory associates for their guidance and collaboration.

Disclosures: **N.G. Raut:** None. **J.M. Reddy:** None. **K. Roden:** None. **D.L. Hynds:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

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Topic: A.04. Axon and Dendrite Development

Support: Strategic Research Foundation Grant-aided Project for Private Universities from Ministry of Education, Culture, Sport, Science, and Technology, Japan (MEXT), 2014-2018 (S1411003).

Title: Correlation analysis of ATP levels and morphological change during neurite extension

Authors: *R. SUZUKI, F. NAGASE, K. HOTTA, K. OKA;
Keio Univ., Kouhoku-Ku, Yokohama, Japan

Abstract: Adenosine triphosphate (ATP) is a major energy source for cells and plays important roles in various physiological phenomena. In neurons, ATP depletion suppresses actin turn-over and long-term ATP depletion causes changes in cellular shape. Furthermore, it is known that

neuronal branching occurs at sites populated by stalled mitochondria. Though these previous researches indicate variation in ATP levels is related to cellular morphological changes, such relationships have never been directly demonstrated under physiological conditions, because simultaneous observation and spatiotemporal quantification of cellular morphology and ATP levels are difficult. In this study, a combination of simultaneous imaging and image processing analysis allowed us to observe and quantify these relationships under physiological conditions in growth cones (GCs) of dorsal root ganglion (DRG) neurons. We classified neurons into two groups according to their behaviors: 'elongating neurons' and 'other neurons', and quantified morphological parameters and ATP levels. GC has two domains: actin-rich 'peripheral domain (P-domain)' and microtubule-rich 'central domain (C-domain)'. ATP levels in P-domain and C-domain had positive correlations between newly generated area and gross size of the domains. Especially, these positive correlations in C-domains were more remarkable in elongating neurons. Also, ATP levels in elongating neurons were higher at C-domain, whereas the other neurons showed the reverse tendency. This trend is also true for newly generated areas. Moreover, Latrunculin A, an inhibitor of actin polymerization, diminished size and motility of P-domain, but not that of C-domain. On the other hands, GCs treated with Oligomycin A which inhibits ATP synthase showed not only decrease in ATP levels, size, and motility at P-domain, but also retraction of C-domain. Therefore, neuronal elongation would needs ATP but not actin polymerizations in P-domain. From the above, our research revealed that ATP levels in GCs are related to its morphological change, and the relationships in C-domain plays grate role in neurite extension.

Disclosures: **R. Suzuki:** None. **F. Nagase:** None. **K. Hotta:** None. **K. Oka:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

Location: Hall A

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Program#/Poster#: 566.24/A24

Topic: A.04. Axon and Dendrite Development

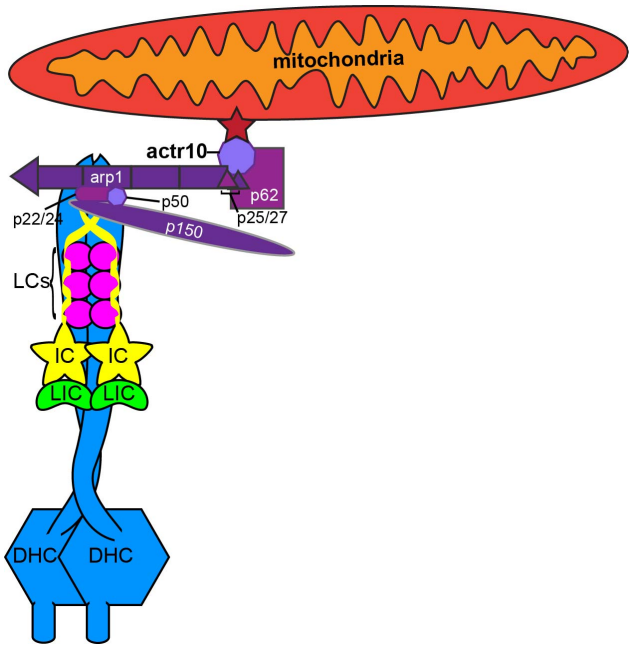
Support: NIH/NINDS Grant 5K99NS086903-01A1

NIH/NICHD Grant 5R01HD072844-03

Title: Regulation of retrograde mitochondrial transport in axons

Authors: *K. DRERUP, S. LUSK, A. NECHIPORUK;
Cell, Developmental and Cancer Biol., Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: The cytoplasmic dynein motor is the primary motor protein complex responsible for retrograde cargo transport in axons. How this single motor moves disparate cargo in a regulated fashion remains largely unknown. We have utilized forward genetics, live imaging and biochemistry to identify a role for a dynein associated protein, Actr10, in the selective retrograde transport of mitochondria. In a forward genetic screen, we isolated a zebrafish mutant with mitochondria rich, swollen axon terminals. Using RNA-seq based analysis, we identified the causative mutation as a T to G change in the start site of the gene encoding Actr10. Actr10 is a component of the dynactin, a large accessory complex oftentimes associated with the cytoplasmic dynein. Actr10 is situated in a "pointed end" region of dynactin which is postulated to function as an adaptor for cargo transport; however, a specific role for Actr10 in retrograde cargo movement in axons has not been elucidated. Using *in vivo* analysis of mitochondrial motility, we found that the mitochondrial accumulation in *actr10* mutant axon terminals was due to a selective defect in the retrograde transport of this organelle. The localization of dynein-dynactin components and other cargos, such as lysosomes, autophagosomes, and activated JNK (c-Jun N-terminal Kinase) was normal in the *actr10* mutants. Additionally, *in vivo* analysis of dynein motility demonstrated that movement of this motor is unaffected with loss of Actr10, arguing for a specific role for Actr10 in mitochondria retrograde movement. Finally, using mitochondrial fractionation and immunoprecipitation, we have shown that loss of Actr10 results in failed dynactin-mitochondrial coupling further supporting a role for this protein in attaching mitochondria to the retrograde motor complex. Together, our data support a model in which Actr10 serves as a unique adaptor which links mitochondria to the retrograde motor complex for retrograde transport and proper positioning in axons.



Disclosures: **K. Drerup:** None. **S. Lusk:** None. **A. Nechiporuk:** None.

Poster

566. Cytoskeletal Functions in Neurodevelopment

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 566.25/A25

Topic: A.01. Neurogenesis and Gliogenesis

Support: National Alliance for Research on Schizophrenia and Depression 2012

Marion G. Nicholson Distinguished Investigator Award from the Brain and Behavior Research Foundation

National Science Foundation Grant IBN-1353724

Title: The roles of CPE and its interactor, $p150^{Glued}$, in regulation of neuronal cytoskeleton and migration

Authors: *C. LIANG[1,2], D. CARREL[1], H. KIM[1], B. L. FIRESTEIN[1];
[1]Cell Biol. and Neurosci., [2]Mol. Biosci. Grad. Program, Rutgers Univ., Piscataway, NJ

Abstract: Carboxypeptidase E (CPE) is a member of carboxypeptidase family that processes various proteins. However, CPE has functions in addition to its carboxypeptidase activity. CPE knockout mice have neurobehavioral deficits, including deficits in learning and memory. They exhibit aberrant neurotransmission and dendritic architecture. Previously, we identified a role for CPE in mediating the effects of nitric oxide synthase 1 adaptor protein (NOS1AP) action on dendritogenesis. It was previously reported that $p150^{Glued}$ and CPE exist in a complex in cultured cells; we now confirm this interaction in mouse brain. Our current study identifies the region in $p150^{Glued}$ that is responsible for CPE binding. In addition, our studies in COS-7 cells suggest that CPE overexpression redistributes endogenous $p150^{Glued}$ from the centrosome and disrupts microtubule organization. As $p150^{Glued}$ is the largest subunit of the Dynactin complex, which is indispensible for the functional motor activity of dynein, we hypothesized that CPE exerts its effect on the cytoskeleton through its interaction with motor protein complexes and/or other microtubule binding proteins. Thus, we extended our studies to assess the role of CPE *in vivo* during the time of cortical neuron migration since this process relies heavily on motor protein complexes and the cytoskeleton. Preliminary data show that knockdown of CPE protein results in disrupted neuronal migration and altered cell morphology in neurons in the cortical plate. Together, our studies provide new evidence for the role of CPE and its interactor, $p150^{Glued}$, in regulating the neuronal cytoskeleton, dendrite morphology, and cortical cell migration.

Disclosures: **C. Liang:** None. **D. Carrel:** None. **H. Kim:** None. **B.L. Firestein:** None.

Poster

567. Development of Neuronal and Circuit Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 567.01/A26

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIH Grant MH104773-02

Title: Regulation of hindbrain spontaneous activity by K2P channels

Authors: *K. DUONG[1], H. WATARI[2], A. TOSE[1], J. GILE[1], M. BOSMA[1];
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Abstract: The developing brain experiences endogenous electrical activity in the absence of any sensory input. This spontaneous activity (SA) has been shown to drive neuronal and circuit development in many areas of the brain. We have reported that in mouse embryonic hindbrain, SA is regulated spatially and temporally. SA initiates from a region along the midline, spreads across hindbrain in the form of propagating waves at E11.5, and retracts back to the initiation zone by E13.5. The mechanism of this retraction is the hyperpolarization of resting membrane potential and concomitant increase in conductance between E10.5-E15.5. Together, these changes decrease cellular excitability, resulting in the cessation of SA by E15.5. We found that membrane hyperpolarization is correlated with the upregulation of a class of resting potassium channels, the two-pore domain potassium channel (K2P). Three types of K2P channels are found in the developing hindbrain: KCNK2, KCNK9, KCNK10. At least 2 of the 3 channels (KCNK2 and KCNK9) are upregulated between E11.5 and E15.5, and KCNK9 is spatially expressed to mediate lateral hyperpolarization. These channels could play the appropriate role of increasing resting conductance and decreasing cellular excitability.

Disclosures: K. Duong: None. **H. Watari:** None. **A. Tose:** None. **J. Gile:** None. **M. Bosma:** None.

Poster

567. Development of Neuronal and Circuit Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 567.02/A27

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: American Hearing Research Foundation Research Grant

Title: An auditory hair cell-specific inducible gene expression system to suppress spontaneous activity in hair cells

Authors: *Y. ASAI[1,2], G. G. S. GÉLÉOC[1,2], J. R. HOLT[1,2];
[1]Neurosci. Dept., Boston Childrens Hosp., Boston, MA; [2]Harvard Med. Sch., Boston, MA

Abstract: Cell type-specific, tightly-regulated, reversible gene expression systems are valuable for interpretation of gene/cell function. We designed a system that allows precise spatiotemporal control of gene expression in hair cells. In the *lac* regulatory system, gene expression is regulated by binding of LacI protein to *lac* operator sequences in promoter regions that flank the transcriptional start site. The regulation is reversible, as addition or removal of the inducer, Isopropyl β-D-1-thiogalactopyranoside (IPTG), which turns on or off gene expression at any point during the animal's life. We engineered this system for use with a modified Myosin7a (*Myo7a**) promoter, whose activity in the inner ear is restricted to hair cells. We tested *lac* operators placed at various positions within the *Myo7a** promoter for regulatability of luciferase gene expression in HeLa cells. After the initial screen, we prepared adenoviral vectors with the optimized *Myo7a** promoter and the coding sequence for GFP and transfected inner ear tissue that expressed LacI. GFP expression was restricted to hair cells and was tightly regulated by IPTG induction. Inner hair cells have spontaneous activity prior to the onset of hearing but the role of the activity is unknown. We hypothesis that spontaneous activity in hair cells may contribute to synaptogenesis and maturation of the peripheral auditory system. To investigate this hypothesis, we generated a transgenic mouse that expressed TREK1 K^+ channels regulated by the *Myo7a** promoter. We found that IPTG induction drove expression of TREK1 potassium currents and clamped the hair cell resting potential near E_{K+}, which effectively silenced the cells. To assay for behavioral consequences of TREK1 expression we measured acoustic startle responses. Administration of IPTG for 3 days, from postnatal day 21 to 24 completely abolished startle responses in TREK1 mice. These results indicate induced expression of TREK1 effectively silenced hair cell electrical activity. This novel mouse model will be used to investigate the role of hair cell activity during inner ear development. Conclusions: 1) The *Myo7a** promoter was regulatable using *lac* operators and IPTG induction. 2) Hair cell expression was confirmed *in vitro* via adenoviral transfection. 3) The *Myo7a** promoter drives TREK1 expression in hair cells of transgenic mice and successfully silenced the cells. We suspect our inducible hair cell-specific promoter and the TREK1 mouse developed for this study will be valuable genetic tools to regulate gene expression and hair cell function *in vivo*.

Disclosures: Y. Asai: None. **G.G.S. Géléoc:** None. **J.R. Holt:** None.

Poster

567. Development of Neuronal and Circuit Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 567.03/A28

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: Monbu Kagaku-Sho of Japan

Title: Optical analysis of developmental changes in oscillatory activity in the embryonic chick olfactory bulb

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[2]Dept. of Nutr. and Dietetics, Kanto-Gakuin Univ, Col. of Nutr., Yokohama, Japan

Abstract: In our previous study (Sato et al., 2007), we applied a multiple-site optical recording technique with a voltage-sensitive dye to the embryonic chick olfactory system and showed that functional synaptic transmission in the olfactory bulb was expressed at around E7. It is known that odor stimuli elicit oscillatory events in the olfactory bulb in various species. In the present study, we found that oscillatory activity was also generated in the chick olfactory bulb during embryogenesis. At the early stages of development (E7-E8), postsynaptic response-related optical signals evoked by olfactory nerve stimulation exhibited a simple monophasic waveform that lasted a few seconds. At the E9 stage, the postsynaptic response-related optical signals became multi-phasic, and these neural responses developed into oscillatory activity around the E10 stage. As development proceeded, the pattern of the oscillatory activity became complicated and long-lasting. The oscillatory activity was restricted to the olfactory bulb, and its spatial pattern was different from that of the propagating wave activity termed the depolarization wave. We examined fundamental characteristics of the oscillatory activity and their developmental dynamics.

Disclosures: K. Sato: None. **Y. Momose-Sato:** None.

Poster

567. Development of Neuronal and Circuit Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 567.04/A29

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Title: Leptin guides chloride homeostasis in the developing rodent hippocampus

Authors: *C. DUMON[1], D. DIABIRA[1], C. PORCHER[1], G. A. WAYMAN[2], I. MEDYNA[1], J.-L. GAIARSA[1];
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Abstract: γ-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the adult brain. GABA controls neuronal excitability, network oscillations dynamic and synaptic plasticity, thereby playing a crucial role in brain functioning. However, at fetal and early postnatal stages, GABA depolarizes and often excites neurons due to an elevated intracellular chloride concentration, and this depolarizing effect is believed to support its multiple neurotrophic actions during development. The sequential expression of two major chloride co-transporters, Na+-K+-Cl- type 1 cotransporter (NKCC1) and K+-Cl- type 2 cotransporter (KCC2) drives the shift of GABAergic responses from depolarizing to hyperpolarizing (D/H) in the developing CNS. But if this sequential expression is crucial for brain functioning, factors that control it remains largely unknown. Leptin is an adipocyte-derived hormone acting on the hypothalamus to reduce food intake and enhance energy expenditure. But there is a growing number of evidences showing that leptin action is not only restricted to metabolism, but also implies a key neurotrophic role in different brain areas. Based on the fact that circulating levels of leptin are developmentally regulated and parallel the D/H shift of GABA, we hypothesized that leptin could be one factor controlling chloride homeostasis in the brain. Here we show that the developmental D/H sequence of GABA is abolished in leptin- (ob/ob) and leptin receptor- (db/db) deficient mice hippocampi. Thus, the reversal potential of GABAA receptor-mediated synaptic currents (EGABA) remains hyperpolarizing throughout postnatal development (from P3 to P15) in db/db and ob/ob mice. Moreover, a brief (2min) application of the specific GABAA receptor agonist isoguvacine (3μM) decreases spiking activity of hippocampal neurons in newborn db/db and ob/ob, while the same application increases spiking activity in WT. We further show that acute administration of leptin induces a depolarizing shift of EGABA. Finally, we also provide data showing that this effect involve a down-regulation of KCC2 activity. These results indicate that high leptin levels controls chloride homeostasis in neonatal neurons and that the decrease to adult leptin level underlies the physiological developmental switch of GABAergic responses.

Disclosures: C. Dumon: None. **D. Diabira:** None. **C. Porcher:** None. **G.A. Wayman:** None. **I. Medyna:** None. **J. Gaiarsa:** None.

Poster

567. Development of Neuronal and Circuit Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 567.05/A30

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: Monbu Kagaku-Sho of Japan

Title: Development of functional synaptic networks in the mouse vagal pathway revealed by voltage-sensitive dye imaging

Authors: *Y. MOMOSE-SATO[1], K. SATO[2];
[1]Dept. of Nutr. and Dietetics, Kanto Gakuin University, Col. of Nutr., Yokohama, Japan;
[2]Komazawa Women's Univ, Fac. of Human Hlth., Tokyo, Japan

Abstract: The vagus nerve (N.X) transfers autonomic input and output information to and from the brainstem, and analysis of the N.X-related brainstem nuclei is the first step to understand the functional organization of the autonomic neuronal circuits. Investigations of the neural network organization have been hampered because conventional electrophysiological means have some technical limitations. In the present study, the multiple-site optical recording technique with a voltage-sensitive dye was used to survey the functional organization of the vagal system in a mouse embryo. Stimulation of the N.X in E11 to E14 mouse embryos elicited optical responses in areas corresponding to the vagal sensory and motor nuclei. Postsynaptic responses in the first-order sensory nucleus, the nucleus of the tractus solitarius (NTS), were identified from E11-E12, suggesting that sensory information was transferred to the brain by this stage. In addition to the NTS, optical responses were identified in the rostral and contralateral brainstem regions, which appeared to correspond to second/higher-order nuclei of the vagus nerve. Postsynaptic responses in the second/higher-order nuclei were detected from E12, suggesting that polysynaptic pathways were functional by this stage. We discuss the results of optical mapping, comparing them with previous findings obtained in chick and rat embryos.

Disclosures: Y. Momose-Sato: None. **K. Sato:** None.

Poster

567. Development of Neuronal and Circuit Excitability

Location: Hall A

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Program#/Poster#: 567.06/A31

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: The G. Harold and Leila Y. Mathers Charitable Foundation

Title: Spontaneous emergence of neuronal groups and attractor dynamics in a spiking model of developing primary sensory cortex

Authors: *T. MICONI, J. MCKINSTRY, G. M. EDELMAN;
Neurosciences Inst., La Jolla, CA

Abstract: A long-standing proposal suggests that sensory neurons organize into coherent, competitive groups, which emerge from attractor dynamics supported by reciprocal connections, and represent stimuli by their collective activity (rather than through the responses of individual cells). Recent observations from multiple sources have provided tantalizing support for this hypothesis. However, whether (and how) neurons develop attractor dynamics remains controversial. Here we describe a computational model of a small patch of primary visual cortex, composed of 100 spiking neurons endowed with spike timing dependent plasticity for lateral and feedforward connections, and all-to-all mutual inhibition. We use state-of-the-art models for neural dynamics (Adaptive-Exponential neurons) and synaptic plasticity (Clopath-Gerstner voltage-based spike timing dependent plasticity). We expose this model to natural images, processed to emulate the operation of retinal cells. We find that the model spontaneously arranges into competitive groups of reciprocally-connected, similarly-tuned neurons, while developing realistic, orientation-selective receptive fields for each individual cell. Neural groups respond in a competitive, all-or-nothing manner, in accordance with experimental data. Crucially, the same groups are observed in both stimulus-evoked and spontaneous (stimulus-absent) activity, confirming the role of internal dynamics in their formation and replicating physiological observations. Mutual connections exhibit the experimentally observed properties of symmetry, sparsity and cliquishness. The final self-organized network is inhibition-stabilized and exhibits attractor dynamics without slowing down network dynamics. Importantly, the development of coherent neural ensembles requires naturalistic stimuli: randomized stimuli (with identical distribution of intensities but no spatial correlations) do not give rise to group formation or attractor dynamics. Our results support the hypothesis that local cortical microcircuits organize into attractor networks that support discrete response patterns (i.e., neuronal groups), and show that known properties of developing cortex, together with exposure to natural stimuli, suffice to explain the emergence of these dynamics.

Disclosures: **T. Miconi:** None. **J. McKinstry:** None. **G.M. Edelman:** None.

Poster

567. Development of Neuronal and Circuit Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 567.07/A32

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIAAA AA015614

Title: Functional serotonin signaling in the hippocampus prior to dorsal raphe maturation in neonatal mice

Authors: *R. A. MORTON[1], Y. YANAGAWA[2], C. VALENZUELA[1];
[1]Neurosciences, Univ. of New Mexico, Albuquerque, NM; [2]Genet. and Behavioral Neurosci., Gunma Univ. Grad. Sch. of Med., Maebashi, Japan

Abstract: During brain development serotonin (5-hydroxytryptamine (5-HT)) plays a major role in cell proliferation, migration, axonal guidance, and circuit wiring. In rodents the first two weeks of postnatal life are developmentally equivalent to the third trimester of human development. Previous studies have shown that serotonin plays a critical role in dendritic development, dendritic length, branching, and spine formation in the hippocampus. Serotonin is produced by neurons located within the raphe nucleus that are highly regulated by local GABA interneurons. The goal of these studies is to characterize the electrophysiological properties of both local GABA and putative serotonin neurons within the dorsal raphe and the functionality of serotonin synapses in the CA1 hippocampal region during the third trimester-equivalent period (post-natal days (P) P5 - P17). To identify GABA neurons, we used a transgenic mouse that expresses the Venus fluorescent protein (developed by Dr. Atsushi Miyawaki at RIKEN, Wako, Japan) driven by the vesicular GABA transporter (VGAT) promoter (Wang et al. 2009). Putative serotonin neurons were identified by their anatomical location and the lack of Venus expression. P5-P7 and P15-P17 pups were used to represent early and late stages of the third trimester equivalent period, respectively. GABA neurons displayed a lower threshold for action potential firing (P5-P7 = 20 pA vs P15-P17 = 50 pA, n=11) and a higher firing rate with a 100 pA current injection (P5-P7 = 17.28 Hz vs P15-P17 = 9.46 Hz, n=11). Spontaneous excitatory post-synaptic currents (sEPSCs) had a frequency of ~1 Hz and a peak amplitude of ~50 pA in both cell types at both ages (n=10 for each). Putative serotonin neurons displayed an increase in the frequency of spontaneous inhibitory post-synaptic currents (sIPSCs) (P5-P7 = 0.9 Hz vs P15-P17 = 4.16 Hz). To test for functional serotonin synapse in the CA1 region of the hippocampus, we utilized another transgenic mouse that expresses channel rhodopsin 2 under the control of the tryptophan hydroxylase 2 (TpH2) promoter, restricting the expression to serotonin neurons only. In the CA1 region of the hippocampus, serotonin is known to potentiate sIPSCs in CA1 pyramidal neurons.

Light induced serotonin release increased the sIPSC frequency by ~2 fold (P5-P7 = 2.4x, P15-P17 = 1.76x, n=7), and induced a tonic current of ~18 pA (P5-P7 = 15.8 pA, P15-P17 = 20.4 pA, n=7) at both ages. Our studies suggest that both GABA and serotonin neurons undergo electrophysiological and synaptic changes during the third trimester equivalent, but serotonin signaling in the CA1 region is functional as early as P5.

Disclosures: **R.A. Morton:** None. **Y. Yanagawa:** None. **C. Valenzuela:** None.

Poster

567. Development of Neuronal and Circuit Excitability

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Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: Boehringer Ingelheim Fonds

Title: Functional dynamics of developing newborn neurons

Authors: ***J. BOULANGER-WEILL**, G. SUMBRE;
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Abstract: During vertebrate embryogenesis and up to adulthood, newborn neurons are continuously added to the existing circuitry. A major challenge in neurosciences is to understand how newborn neurons functionally incorporate into mature neuronal circuits. To this end, we have used the retino-tectal system of the zebrafish larva to monitor the developing activity of newborn neurons and the surrounding matured network. Due to the zebrafish larva's small size, transparency, rapid external development and the genetic advantages that the model presents, it was possible to label both newborn and matured circuit tectal neurons, and monitor their developing activity dynamics by means of two-photon calcium imaging and optogenetics, in an intact non-anesthetized and non-paralyzed vertebrate, during four consecutive days after the neurons were born. At the onset of labeling (day 1), labeled newborn neurons displayed an undeveloped dendritic arbor and their cell identity was not yet established (excitatory or inhibitory). Within a 4-days period their dendritic arborization increased by ten-fold and matched described mature morphological subtypes (Nevin et al., BMC Biology, 2010). Rapidly (day1) newborn neurons exhibited spontaneous activity events although robust correlated activity with their matured surrounding neighbors emerged 2 days later (day3). Certain newborn neurons progressively incorporated into local assemblies forming part of the retinotopic map of the optic tectum (Romano et al, Neuron 2015), while others incorporated into spatially sparse circuits.

Interestingly newborn neurons already displayed visually induced responses from the onset of labeling. These responses became more robust and neuronal tuning became sharper (receptive field and direction selectivity) matching those of the matured population after four days. Overall, our results suggest that newborn neurons first choose pre-synaptic partners before integrating into tectal micro-circuits. We are now investigating whether newborn neurons first establish their functional identity and then choose their tectal partners accordingly, or whether they incorporate within a tectal circuit later adopting a functional identity matching the matured recruiting circuit. Understanding the functional dialogue between newborn and matured neurons may open the way for the development of novel techniques for stem-cell brain repair.

Disclosures: J. Boulanger-Weill: None. **G. Sumbre:** None.

Poster

567. Development of Neuronal and Circuit Excitability

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Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: KAKENHI 15K14327

KAKENHI 23680038

Sumitomo Foundation

JST PRESTO

RIKEN

Title: Spontaneous neuronal activity is required for dendrite pruning of olfactory mitral cells in early postnatal development

Authors: *S. FUJIMOTO[1], Y. MUROYAMA[2], T. SAITO[2], T. IMAI[1];
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Abstract: Neuronal circuits are sculpted by pruning excessive axons and dendrites of neurons in early postnatal stages. In the olfactory system, each mitral cell initially connects multiple primary dendrites to multiple glomeruli, and then eliminates all but one primary dendrite during the first postnatal week, eventually forming a single primary dendrite which connects to a single

glomerulus. This observation indicates that the wiring specificity of primary dendrite is established by a postnatal pruning process. However, the mechanisms of selective dendrite pruning remain largely unknown. Here we investigated the involvement of neuronal activity by overexpressing Kir2.1 to silence neuronal excitability in mitral cells. We found that overexpression of Kir2.1 severely perturbed the pruning of primary dendrites as well as the extension of lateral dendrites. In contrast, mice expressing tetanus toxin in all olfactory sensory neurons showed only minor delays in the pruning process, which is most likely due to an indirect consequence of poor suckling. These results suggest that olfactory sensory neuron-independent spontaneous neuronal activity regulates selective dendrite pruning in mitral cells. We next performed two-photon calcium imaging of acute olfactory bulb slices to clarify the nature of spontaneous activity during development. We observed propagating waves of activity across glomeruli before and during dendrite pruning process (P0-3). Pharmacological experiments revealed that gap junctions are required to propagate the spontaneous activity in the olfactory bulb. The pattern of spontaneous activity gradually became decorrelated after the pruning period. Taken together, our data suggest that sensory stimuli-independent spontaneous activity regulates precise dendritic connections. This propagating spontaneous activity may have an instructive role in the dendrite pruning process.

Disclosures: **S. Fujimoto:** None. **Y. Muroyama:** None. **T. Saito:** None. **T. Imai:** None.

Poster

567. Development of Neuronal and Circuit Excitability

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Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: JST PRESTO

Sumitomo Foundation

KAKENHI (23680038)

RIKEN

Title: Developmental changes in spontaneous activity in the neonatal mouse olfactory bulb *in vivo*

Authors: ***M. N. LEIWE**, T. IMAI;
Lab. For Sensory Circuit Formation, Kobe, Japan

Abstract: The correct formation of neural circuits is vital for the function of the brain, this is achieved by both the correct outgrowth and pruning of neurites (axons and dendrites). In the mouse olfactory bulb (OB), Mitral and Tufted cells (M/T cells) are the principal output neurons, receiving input from Olfactory Sensory Neurons (OSNs) in the glomerular layer of the OB, and projecting axons to the olfactory cortex. During postnatal development, M/T cells refine their dendrites from connecting to multiple glomeruli (Postnatal days 0-4/5) to a single primary dendrite connecting to a single glomerulus ≥P6). Genetic experiments in our lab uncovered a critical role for non-sensory (spontaneous) activity in shaping this refinement. However, the nature of this spontaneous activity is unknown. Therefore our aim was to uncover the nature, source, and role of spontaneous OB activity and to provide insight into the rules that regulate M/T dendrite refinement, i.e. how M/T cells determine the winning (surviving) dendrite. To this end, we directly recorded spontaneous activity in the neonatal mouse OB using 2-Photon *in vivo* Ca2+ imaging with the genetically encoded calcium indicators GCaMP3/6f expressed in either M/T cells or OSNs across the early postnatal days (up to P10). We detected spontaneous activity in M/T cells in awake mice, but not in OSNs, suggesting that it is intrinsic to the OB, consistent with our previous genetic experiments. We also observed a change from a correlated wave-like pattern (P2-3), to random decorrelated activity patterns (P4-10) within M/T cells. This was quantified with Spike Time Tiling Co-efficient (STTC) analysis which demonstrated a distance dependent correlation pattern at P2-3, an intermediate stage at P4-5, and a purely random pattern at P10. These results suggest that the wave-like spatiotemporal patterns of spontaneous activity in early postnatal period (P2-3) may be important in shaping the innervation patterns of the dendrites of M/T cells.

Disclosures: **M.N. Leiwe:** None. **T. Imai:** None.

Poster

567. Development of Neuronal and Circuit Excitability

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Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: The National Institute of Health and Medical Research

MESER

Title: *In vivo* expression of Pro-Brain-Derived Neurotrophic Factor (proBDNF) alters Glutamate/GABA balance and increases seizure susceptibilty

Authors: *B. RIFFAULT, C. DUMON, N. KOURDOUGLI, N. FERRAND, J.-L. GAIARSA, C. PORCHER;
INMED, Marseille, France

Abstract: The Brain Derived Neurotrophic Factor (BDNF) is synthesized as a precursor, namely proBDNF, which can be processed into mature BDNF (mBDNF). ProBDNF, signaling through p75NTR is biologically active and are assumed to produce opposing physiological responses to mBDNF. Accumulating evidences indicate that impairment of proBDNF proteolysis may account for the emergence of neurological disorders. These findings support the view that the relative availability of mBDNF and proBDNF forms is an important mechanism underlying brain circuit formation and cognitive functions. Here we show that *in vivo* cortical expression of a cleavage resistant proBDNF isoform (CR-proBDNF) results in aberrant dendritic complexity in cortical pyramidal neurons, impaired excitatory/inhibitory balance that in turn leads to cortical network hyper excitability *in vitro*. The latter was confirmed *in vivo* as we find that CR-proBDNF rats are highly susceptible to epileptic seizure. Altogether these results suggest that neuronal disorders triggered by alterations in BDNF processing play a key role in cortical network wiring and shed light on the involvement of proBDNF/p75NTR signaling in the development of epilepsy.

Disclosures: B. Riffault: None. **C. Dumon:** None. **N. Kourdougli:** None. **N. Ferrand:** None. **J. Gaiarsa:** None. **C. Porcher:** None.

Poster

567. Development of Neuronal and Circuit Excitability

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Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NTU

MOST-103-2311-B-002-026-MY3

Title: Calcium binding to Synaptotagmin III regulates patterned spontaneous activity during visual circuit development

Authors: *W.-C. SHU[1], Y.-T. HUANG[1], S.-Y. KAO[1], Y.-T. HSIAO[1], C.-T. WANG[1,2,3,4];
[1]Inst. of Mol. and Cell. Biol., [2]Dept. of Life Sci., [3]Neurobio. and Cognitive Sci. Ctr., [4]Genome and Systems Biol. Program, Natl. Taiwan Univ., Taipei, Taiwan

Abstract: Patterned spontaneous activity in the developing retina, termed retinal waves, appears during the critical period of visual circuit refinement. Stage II retinal waves (P0-P9 in rats), essential for eye-specific segregation of retinogeniculate projection, are initiated by starburst amacrine cells (SACs) releasing neurotransmitters to other SACs and retinal ganglion cells (RGCs). Our previous studies found that the expression level of Synaptotagmin III (Syt III) was significantly increased in the RGCs during P4 to P6, i.e., the critical period of eye-specific segregation. We also found that Syt III regulates the kinetics of calcium-dependent exocytosis through calcium binding to the C2A and C2B domains. However, how calcium binding to Syt III plays a role in regulating stage II waves remains unknown. In this study, we combined molecular perturbation and live calcium imaging to detect the function of Syt III-calcium binding sites in regulating stage II waves. By using the cell-type specific promoters (pBrn3b for RGCs and pmGluR2 for SACs), we overexpressed Syt III or its mutant with the abolished calcium binding sites in the C2AB domains (Syt III-D386,520N). We found that overexpressing wild-type Syt III in RGCs increased the frequency of wave-associated spontaneous calcium transients compared to the control. By contrast, overexpressing Syt III-D386,520N in either SACs or RGCs decreased calcium transient frequency compared to wild-type Syt III. These results suggest that Syt III may regulate the kinetics of retinal waves through calcium binding to its C2AB domains.

Disclosures: W. Shu: None. **Y. Huang:** None. **S. Kao:** None. **Y. Hsiao:** None. **C. Wang:** None.

Poster

567. Development of Neuronal and Circuit Excitability

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Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: MOST-103-2311-B-002-026-MY3

Title: Phosphorylation of cysteine string protein-alpha regulates retinal waves during development

Authors: C.-F. CHEN[1], Y.-T. HSIAO[1], T.-Y. WO[1], *C.-T. WANG[1,2,3,4];
[1]Inst. of Mol. and Cell. Biol., [2]Dept. of Life Sci., [3]Neurobio. and Cognitive Sci. Ctr., [4]Genome and Systems Biol. Program, Natl. Taiwan Univ., Taipei, Taiwan

Abstract: During a developmental critical period, the binocular visual system displays a robust patterned spontaneous activity termed “retinal waves”, which are shown essential for visual

circuit refinement. These waves are initiated by presynaptic starburst amacrine cells (SACs) releasing neurotransmitters onto other SACs and retinal ganglion cells (RGCs) through calcium-regulated exocytosis. Cysteine string protein (CSP) is found to ensure correct folding of the exocytotic machinery and can be phosphorylated by protein kinase A (PKA), whose activity demonstrates correlated oscillations with retinal waves. However, it is unknown whether retinal waves can be regulated by PKA-mediated CSP phosphorylation in SACs. In this study, we combined molecular perturbation, exo vivo transfection, and live imaging to investigate how CSP phosphorylation in SACs regulates the spatiotemporal properties of retinal waves. We found that CSP was expressed in the inner plexiform layer (IPL) of the neonatal rat retina and the dominant isoform in the developing rat retina was CSPα. Further immunostaining of dissociated retinal cells confirmed that the expression of CSP was localized to presynaptic SACs, suggesting that CSP involves in regulating neurotransmitter release from SACs. To investigate whether phosphorylation of CSPα in presynaptic SACs affects retinal waves, we targeted gene expression to SACs by the metabotropic glutamate receptor type II promoter. After overexpression of CSP or its phosphomutants in SACs, subsequent calcium imaging was performed in the RGC layer to detect the spatiotemporal properties of wave-associated spontaneous calcium transients. We found that the frequency of calcium transients was significantly decreased by the phosphodeficient mutant (CSPα-S10A), but not by the wild-type CSPα (CSPα-WT) or the phosphomimetic mutants (CSPα-S10D and CSPα-S10E) compared to the control. These CSPα phosphomutants had a relatively minor effect on the spatial correlation of spontaneous calcium transients. Therefore, our results suggest that phosphorylation of CSPα may play an important role in regulating the temporal properties of retinal waves.

Disclosures: **C. Chen:** None. **Y. Hsiao:** None. **T. Wo:** None. **C. Wang:** None.

Poster

567. Development of Neuronal and Circuit Excitability

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Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: FAPESP

UFABC

Title: Evaluation of Cx36 and Cx45 expression during postnatal development of rats hippocampus

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Abstract: Spontaneous activity patterns emerge in neurons during maturation process in several central nervous system regions. In the course of postnatal development of hippocampus, a number of neurons display spontaneous activity characterized by increased of calcium dynamics and voltage changes. These events present characteristics such as coherent and recurrent electrical activity among hippocampal neurons (synchronous plateau assemblies, SPAs, and giant depolarizing potential, GDPs). The spontaneous activity of hippocampal neurons modulates the proper conduct of neuronal connections during local network shaping. Thus, some studies have been demonstrated that gap junction (GJ) is essential for SPAs generation and propagation. GJ allow the passage of small molecules up to 1 kDa. GJ channels are made of protein subunits called connexins (Cx). Our previews results demonstrated the dynamics changes of transcript and protein of Cx36 and Cx45 during postnatal development. Interesting, Cx36 expression was higher in hippocampus at P5 (2^1.96= 3.89 fold-expression, P<0.001) and P10 (2^1.71= 3.27 fold-expression, P<0.01) when compared with adult animal (P60). Similarly, our results indicated that Cx45 is highly expressed during all analyzed postnatal periods of hippocampus (P0:2^2.74= 6.7 fold-expression, P<0.0001; P5: 2^2.73= 6.63 fold-expression, P<0.0001; P10: 2^2.25= 4.75 fold-expression, P<0.0001). Likewise, Cx36 protein levels are found highly concentrated during early postnatal periods (P0:553%, P<0.01; P5:447%, P<0.05) when compared with P60. Nevertheless, Cx45 protein levels are found less concentrated during this period (P5:55%, P<0.01; P10:60%, P<0.05). Taking these results into account, neuronal GJ made by Cx36 can be important modulators of spontaneous activity propagation during activity-dependent period of hippocampus development.

Disclosures: G.S. Vilar Higa: None. **E.R. Kinjo:** None. **A.H. Kihara:** None. **B.A. dos Santos:** None. **F. Alvez:** None.

Poster

567. Development of Neuronal and Circuit Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 567.15/A40

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: K12GM085897

NINDS Grant F31NS081805

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McNair Foundation

Title: Odor activation domains of inhibitory neurons expand with neuronal maturation

Authors: *K. B. QUAST[1], I. GARCIA[2], B. R. ARENKIEL[3];
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Abstract: Sensory maps are created by neuronal responses that vary with their anatomical position, so that representations of the external world are systematically organized within the structure of the brain. Current understanding of cortical sensory maps is that they are sculpted and refined throughout development and/or sensory experience. However, this model is largely derived from investigations into patterns of excitatory cell responses. Taking advantage of the mouse olfactory bulb, where ongoing neurogenesis supplies new inhibitory granule cells into existing circuitry, we isolated the development of sensory evoked activation domains of an inhibitory network. Using *in vivo* calcium imaging of odor responses of the entire dorsal olfactory bulb, we compared functional responses of genetically defined populations of both maturing and established granule cells. We found that in contrast to the activity-dependent refinement and pruning observed for excitatory maps, we see an expansion in the odorant specific activated domains of inhibitory neurons. These data describe the development of an inhibitory sensory map, highlighting the differences between previously described excitatory maps.

Disclosures: K.B. Quast: None. **I. Garcia:** None. **B.R. Arenkiel:** None.

Poster

567. Development of Neuronal and Circuit Excitability

Location: Hall A

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Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: FP7-ERC ‘GABA Networks’ grant (#242842)

Horizon 2020 grant GABACODEV (#660795)

Title: GABAergic hub neurons in the developing entorhinal cortex

Authors: *L. MODOL VIDAL[1], V. SOUSA[2], A. MALVACHE[1], P. GUIGUE[1], T. TRESSARD[1], A. BAUDE[1], R. COSSART[1];
[1]INMED, INSERM U901, marseille, France; [2]INMED, INSERM U901, Marseille, France

Abstract: Coordinated neuronal activity is essential for the development of cortical circuits. GABAergic hub neurons that function in orchestrating early neuronal activity through a widespread net of postsynaptic partners are therefore most likely critical players in the establishment of functional networks. So far, evidence for hub neurons has been achieved in the hippocampus where an early birthdate delineates a subgroup of hub cells. Whether hub cells also exist in the neocortex remains unknown. This is an important issue given that both structures share common developmental programs including a similar sequence for the emergence of population coherence, but also since recent evidence indicates important differences especially regarding the origin of GABAergic neuron diversity. We decided to examine this issue in the entorhinal cortex, the major input region to the hippocampus. To this aim, we used an unbiased approach that identifies operational hub neurons through targeted patch-clamp recordings of high functional connectivity degree neurons in living slices. Further, as spatial origin is a determinant hallmark of selective differentiation for cortical interneurons, we also used the *5-HT3aR-BAC*^{EGFP} and *Lhx6Cre::RCE* mice to differentiate among caudal and medial ganglionic eminences-derivate interneurons, to characterize whether or not spatial origin is critical in the generation of cortical hub cells. Similarly as in the hippocampus, developing entorhinal cortex displays a scale-free organization with hub neurons being GABAergic cells that often display characteristic morphophysiological properties.

Disclosures: **L. Modol Vidal:** None. **V. Sousa:** None. **A. Malvache:** None. **P. Guigue:** None. **T. tressard:** None. **A. baude:** None. **R. Cossart:** None.

Poster

567. Development of Neuronal and Circuit Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 567.17/A42

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: CIHR

NSERC

Title: Depolarizing $GABA_A$ transmission restrains excitatory synapse formation in the developing hippocampus

Authors: *C. K. SALMON[1], H. PRIBIAG[2], S. CAMERON[3], V. MAHADEVAN[4], D. STELLWAGEN[2], M. WOODIN[4], K. MURAI[2];
[1]Ctr. For Res. In Neurosci., Montreal, QC, Canada; [2]McGill, Montreal, QC, Canada; [3]UC Davis, Davis, CA; [4]Univ. of Toronto, Toronto, ON, Canada

Abstract: GABA is the main inhibitory neurotransmitter in the mature brain, but has the distinct property of depolarizing neurons in the immature brain. Depolarizing $GABA_A$ transmission is implicated in glutamatergic synapse formation, however due to GABA's many roles in central nervous system development, its precise role in glutamatergic synapse formation remains to be fully delineated. Here we addressed the importance of depolarizing $GABA_A$ transmission for glutamatergic synapse development in hippocampal CA1 pyramidal neurons. Based on the expression profile of K^+-Cl^- co-transporter 2 and changes in GABA reversal potential, we pinpointed the timing of the switch from depolarizing to hyperpolarizing $GABA_A$ transmission in CA1 neurons in organotypic hippocampal slice culture. Remarkably, prior to the switch, pharmacological blockade of depolarizing $GABA_A$ transmission increased spine density, whereas promoting depolarizing $GABA_A$ transmission decreased spine density. The increase in spine density corresponded to increased mESPC frequency. Interestingly, when slices were allowed to recover from the pharmacological manipulations, the changes in excitatory synapses were sustained for more than a week. Together, these findings suggest that depolarizing $GABA_A$ transmission plays a critical role in shaping connectivity during postnatal hippocampal development by restraining gluatmatergic synapse formation. To determine whether this is the case *in vivo,* we have developed tools to disrupt $GABA_A$ transmission with temporal precision in the living brain during development. We placed a dominant negative Gamma 2 $GABA_A$ receptor subunit under control of the TetOn tetracycline transactivator system for use with *in utero* electroportation. This approach provides tightly controlled expression of dominant negative Gamma 2 in neurons. Furthermore, we designed and screened 6 artificial micro RNAs targeting the Gamma 2 subunit and found that all of these decreased the number of Gamma 2 puncta as well as Beta 3 $GABA_A$ receptor subunit puncta. Moving forward, we will use these tools to inhibit depolarizing $GABA_A$ transmission *in vivo* to assess its role in glutamatergic synapse formation in a temporally specific manner.

Disclosures: C.K. Salmon: None. **H. Pribiag:** None. **S. Cameron:** None. **V. Mahadevan:** None. **D. Stellwagen:** None. **M. Woodin:** None. **K. Murai:** None.

Poster

567. Development of Neuronal and Circuit Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: Medical Research Council New Investigator Grant

Title: NMDA receptor-based template networks of the developing neocortex

Authors: *M. C. ASHBY, S. R. HULME, J. L. ROZAS;
Univ. of Bristol, Bristol, United Kingdom

Abstract: Experience-dependent synaptic plasticity drives the functional maturation of the mammalian neocortex. This type of plasticity usually requires activity of, and often modifies, existing synaptic partners within a pre-existing neuronal network. As such, the earliest-emerging neuronal networks can be thought of as a template that is subsequently modified by experience-dependent plasticity. The properties of these template networks will therefore constrain, or at least strongly influence, the possible effects of subsequent experience-dependent processes. There is significant evidence that NMDA receptors (NMDARs) play a prominent role in the early postnatal development of synapses. In particular, silent, NMDAR-containing synapses are known to be converted to functional, AMPA receptor-containing synapses in an experience-dependent manner. Here, to investigate the properties of emergent template networks, we have analysed the development of NMDAR-based synaptic connectivity in the early stages of postnatal development in the barrel cortex. Using two-photon glutamate uncaging to photostimulate individual neurons, we assessed the of rate of NMDAR-based synaptic connectivity, and the characteristics of those synapses, between layer 4 neurons in acutely-prepared slices from 4 to 10 day old mice. We found that, on top of slowly developing increase in connectivity over the postnatal period, there is a transient burst of NMDAR-based synapses that precedes the normal time window for classical synaptic unsilencing. Unexpectedly, the emergence of this burst of NMDAR-containing synapses is dependent on sensory experience through the whiskers. In contrast, we found that sensory experience has no effect on the postnatal development of passive electrical properties and excitability of the neurons. At these early developmental stages, the layer 4 neurons, which are stellate cells, almost completely lack dendritic spines. Therefore, to assess the role of NMDAR location in driving early synapse formation, we mapped the distribution of NMDARs on the dendritic branches of layer 4 neurons using brief two-photon glutamate uncaging to replicate synaptic events. The emergence of silent and functional synapses on dendritic shafts and on newly-formed spines was shows highly non-random spatial and temporal bias that likely contributes to the maturation of the earliest template networks.

Disclosures: **M.C. Ashby:** None. **S.R. Hulme:** None. **J.L. Rozas:** None.

Poster

568. Central Nervous System Regeneration

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 568.01/A44

Topic: A.07. Transplantation and Regeneration

Support: NIH/NEI grant EY011640

NIH/NEI Core Grant P30 EY003039

Research to Prevent Blindness

Title: Neurogenin brings about photoreceptor-like cells in chick Müller glial cell culture

Authors: R.-T. YAN, L. HE, *S.-Z. WANG;
Univ. Alabama, Birmingham, Birmingham, AL

Abstract: Restoring vision through regeneration of the retina is hampered by the lack of means to activate endogenous progenitor cells to produce a sufficient number of photoreceptors. Recent advances in research of retinal regeneration in fish and of adult neurogenesis in the mammalian brain have heightened the expectation of Müller glia as potential endogenous progenitors for photoreceptors. A critical barrier persists. Thus far, Müller glia of high vertebrates have been largely unresponsive to various experimental manipulations, with few, in any, photoreceptor cells being generated. This study tested whether photoreceptor-like cells would be generated in chick Müller glia cell culture reprogrammed with proneural gene neurogenin. Müller glia cell culture was established with functionally mature retina isolated from day 19 chick embryos. During dissection, the peripheral region of the retina was removed to minimize potential contamination by progenitor cells at the ciliary margin. Passage one culture was infected with RCAS retroviruses expressing neurongenin1 (ngn1), ngn3, or GFP as control. Analysis with immunocytochemistry and cell morphology showed cells positive for visinin, a calcium-binding protein of photoreceptor cells, in cultures infected with RCAS-ngn1 or RCAS-ngn3, but not in the control. Visinin+ cells exhibited morphologies typical of young photoreceptor cells - a compact cell body with a thin process on one side and a short, inner-segment-like compartment on the other. The cultures were also examined with RA4 antibody, which labels retinal ganglion cells and some unidentified progenitor/precursor cells. While RA4+ cells were present in all cultures, RA4+ cells with neuronal morphologies were only present in cultures infected with

RCAS-ngn1 or RCAS-ngn3, with those in the control culture overtly maintaining morphology of Müller glia. Our data show that photoreceptor-like cells could rise de novo in Müller glia cell cultures when reprogrammed with ngn1 or ngn3 and suggest a possibility of using ngn1 or ngn3 to guide Müller glia towards the regeneration of photoreceptors and ganglion cells as well.

Disclosures: **R. Yan:** None. **L. He:** None. **S. Wang:** None.

Poster

568. Central Nervous System Regeneration

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Support: NIH R01 EY024481

NIH P50 HD 018655

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SNSF PBBEB-146099, -155299

Title: Presynaptic zinc regulates optic nerve regeneration: role of ZnT-3 and nNOS

Authors: ***Y. LI**[1,2], K. YUKI[1], L. ANDEREGGEN[1], M. ASDOURIAN[1], M. HERSHFINKEL[3], S. J. LIPPARD[4], P. A. ROSENBERG[1], L. I. BENOWITZ[1];
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Abstract: Retinal ganglion cells (RGCs), the projection neurons of the eye, cannot regenerate their axons following damage to the optic nerve and undergo delayed cell death. Consequently, victims of traumatic or ischemic nerve damage or individuals with degenerative diseases such as glaucoma suffer lifelong visual losses. Zinc is essential for many cellular functions but also

contributes to neuronal death in hypoxic-ischemic injury and other conditions. We reported previously that, shortly after injury to the optic nerve (nerve crush, NC), levels of free zinc (Zn2+) increase rapidly in synapses of the inner plexiform layer (IPL) of the retina, with amounts within RGCs increasing more slowly. Chelating Zn2+ leads to enduring survival of many RGCs as well as extensive axon regeneration (Li et al., SfN Abstract 399.19, 2014). The present experiments explored the mechanisms underlying presynaptic Zn2+ accumulation. We found that levels of the vesicular Zn2+ transporter ZnT-3 increase greatly in terminals of retinal interneurons within a day after NC in a laminar pattern similar to that of Zn2+ itself. Deletion of slc30ac, the gene encoding ZnT-3, nearly eliminated Zn2+ accumulation in the IPL and in RGCs, and promoted both RGC survival and axon regeneration. Because reactive nitrogen species can liberate Zn2+ from metallothioneins, we also investigated the role of nitric oxide (NO) in presynaptic Zn2+ accumulation. Deletion of nos1, the gene encoding neuronal NO synthase (nNOS), eliminated the Zn2+ signal in the mouse retina after NC. Similar results were obtained with the NO scavenger PTIO (2-phenyl-4,4,5,5-tetramethylimidazoline-1-oxyl-3-oxide) or the nNOS-selective inhibitor L-NPA (Nω-propyl-L-arginine). Conversely, the NO donor DETA-NONOate ((Z)-1-[N-(2-aminoethyl)-N-(2-ammonioethyl)amino]diazen-1-ium-1,2-diolate) caused Zn2+ to accumulate in the retina in the absence of NC. Combined with our previous results, these findings show that ZnT-3 and nNOS are required for presynaptic accumulation of Zn2+ in the retina after optic nerve injury, a key step in the suppression of RGC survival and axon regeneration.

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Poster

568. Central Nervous System Regeneration

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: A.07. Transplantation and Regeneration

Support: NIH EY13879

Title: Cadherin expression in normal and regenerating adult zebrafish retinas

Authors: S. BHATTARAI[1], A. SOCHACKA-MARLOWE[1], N. WANG[1], K. FORKAPA[1], R. LONDRAVILLE[1], *Q. LIU[2];
[1]Biol., [2]Univ. Akron, Akron, OH

Abstract: We examined mRNA expression of two classical cadherins (*cadherin-6*, *cadherin-7*) and two delta protocadherins (*protocadherin-17* and *protocadherin-19*) in normal and regenerating (1 day to 3 weeks post optic nerve injuries) adult zebrafish retinas using *in situ* hybridization and qPCR methods. Cadherins are calcium-dependent cell adhesion molecules that play important roles in eye development in both invertebrate and vertebrate species. Our knowledge of cadherins expression and function in developing vertebrate retinas is extensive, but little is known about their expression in normal and regenerating retinas of adult organisms. We found that all four cadherins are mainly expressed in the retinal ganglion cell layer (GCL) and/or inner nuclear layer (INL) of the normal retinas. Following optic nerve crush, expression of these four cadherins showed distinct and time-dependent changes in the regenerating retinas. Increased expression of *cadherin-6* (in the GCL) and *cadherin-7* (in the inner most portion of the INL) in a subset of cells became obvious 1 week after the optic nerve lesion, and the increased expression lasted for another week before returning to control levels 3 weeks following the optic nerve crush. Expression of *protocadherin-17* and *protocadherin-19* in the GCL was apparently decreased after the optic nerve lesion. The decrease in their expression became detectable 1 day after the injury, and became more pronounced in retinas harvested 3 days to 2 weeks post optic nerve crush. Expression of both *protocadherins* returned to control levels 3 weeks after the optic nerve crush. Our results suggest that cadherins may play differential roles in the regeneration of the zebrafish retina. *Bhattarai and Sochacka-Marlowe contributed equally to this project. This study was supported by NIH EY13879 (QL)

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Poster

568. Central Nervous System Regeneration

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Topic: A.07. Transplantation and Regeneration

Support: NIH NS 055976

The Craig H. Neilsen Foundation 224125

Title: After spinal cord injury extracellular cues affect the dynamics of local protein synthesis machinery in regenerating central nervous system axons

Authors: *R. SACHDEVA[1], M.-K. MCMULLEN[1], J. L. TWISS[2], J. D. HOULÉ[1];
[1]Neurobio. and Anat., Drexel Univ. Col. of Med., Philadelphia, PA; [2]Dept. of Biol. Sci., Univ. of South Carolina, Columbia, SC

Abstract: Peripheral nerve grafts (PNGs) support significant regeneration of central nervous system (CNS) axons after spinal cord injury (SCI) in rats, yet most axons fail to leave the PNG when reapposed to spinal cord tissue across a lesion site. Intra-axonal localization of mRNAs and protein synthesis machinery (PSM) generates proteins locally, which the regenerating axons likely use to fine tune the spatiotemporal response to extracellular stimuli. Here we examine regenerating CNS axons for the presence of several key components of PSM and whether their levels change when axons are exposed to the injured spinal cord. Ascending sensory axons after lower thoracic spinal cord transection regenerated into PNGs for different timepoints: Group 1 rats were euthanized at 3 weeks and Group 2 rats at 7 weeks post grafting to compare axons when they are actively growing vs. when they are stalled at the distal end of the PNG, respectively. To analyze whether a second injury to axons elevates levels of PSM, the distal PNG end was cut at 7 weeks (in Group 3 rats). To analyze effects of the injured spinal cord environment, the distal end of PNGs was cut at week 7 and reapposed to spinal cord treated with ChondroitinaseABC or Penicillinase (control) in Groups 4 and 5 respectively. Using immunofluorescence and confocal microscopy, we analyzed the intra-axonal levels of eIF4E-binding protein-1 (4EBP1), phospho-4EBP1, eIF2α, phospho-eIF2α, and phospho-ribosomal protein S6 within neurofilament positive axons. We report that regenerating axons contain PSM components during growth, but the PSM levels are reduced when axons stop growing at the distal end of the PNG. Re-injury of these stalled axons increases axonal localization of the PSM proteins. Preliminary results suggest that re-apposition of the PNG to the injured CNS environment affects the levels of PSM. Our results suggest that CNS axons are capable of local translation to modulate their local protein repertoire during regeneration. This response could be shaped by local extracellular cues that can ultimately promote or inhibit regeneration. A better understanding of these mechanisms may provide future targets to prevent regeneration failure and improve recovery after SCI.

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Poster

568. Central Nervous System Regeneration

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 568.05/A48

Topic: A.07. Transplantation and Regeneration

Title: E6020 as a modulator of immune-mediated gliogenesis

Authors: *L. M. MILICH[1], J. S. CHURCH[2], P. POPOVICH[2], D. M. MCTIGUE[2]; [1]Neurosci., The Ohio State Univ. Wexner Med. Ctr., Norton, OH; [2]Neurosci., The Ohio State Univ. Wexner Med. Ctr., Columbus, OH

Abstract: Oligodendrocytes (OLs), the myelinating cells of the CNS, are vital to axon conductance and integrity but can become damaged during CNS injury and disease. As post-mitotic cells, OLs in the adult CNS are replaced by an endogenous population of oligodendrocyte progenitor cells (OPCs). Following injury or disease in the CNS, various inflammatory mechanisms have been shown to influence OPC and OL responses. Our lab has previously investigated activation of innate immune Toll-like Receptors (TLRs) in the healthy adult rat spinal cord and found that activation of TLR4 by intraspinal microinjection of lipopolysaccharide (LPS) induced robust OPC proliferation and oligodendrogenesis. LPS treatment also induced microglial activation and damaged gray and white matter around the injection site. However, due to its pathogenic nature, the use of LPS (endotoxin) as an oligogenic therapeutic will likely never be approved for use in humans. Therefore, in the current study, we investigated the oligogenic potential of E6020; a less potent, synthetic (non-pathogenic) TLR4 agonist. We hypothesized that E6020 activates microglia/macrophages and induces OPC proliferation and oligodendrogenesis. E6020 treatment of bone marrow derived macrophages and RAW-Blue™ cells *in vitro* elicited an increase in proinflammatory cytokine production and NF-κB activation similar to LPS. Intraspinal E6020 microinjection in adult Sprague-Dawley rats induced microglia/macrophage activation by 24 hours that increased through 7 days. A robust increase in proliferating OPCs was also observed at 7 days with E6020 treatment. E6020 induced significantly less axon/myelin damage than LPS, demonstrating its reduced pathogenic nature. Ongoing studies are investigating the oligogenic potential of intraspinal E6020 treatment after lysolecithin administration to determine E6020s effect on a demyelinating lesion. The results of this study may help elucidate a novel method of promoting oligodendrogenesis within the CNS, which could be used to promote oligodendrocyte replacement and recovery following trauma or demyelinating disease.

Disclosures: **L.M. Milich:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Eisai. **J.S. Church:** None. **P. Popovich:** None. **D.M. McTigue:** None.

Poster

568. Central Nervous System Regeneration

Location: Hall A

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Topic: A.07. Transplantation and Regeneration

Support: ERC, project VASNICHE

Title: Structural regeneration and functional restoration of the adult dentate gyrus after catastrophic granule cells death

Authors: *T. LICHT[1], T. KREISEL[2], B. WOLF[2], G. ROTHE[2], E. KESHET[2];
[1]Developmental biology and cancer research, The Hebrew Univ. of Jerusalem, Jerusalem, Israel;
[2]Developmental Biol. and Cancer Res., The Hebrew Univ., Jerusalem, Israel

Abstract: The adult hippocampus maintains the capacity to generate new neurons throughout life but its normal neurogenic output is rather low and progressively declines with age. The issue whether this neurogenic potential may suffice for recovery from a catastrophic damage associated with massive neuronal loss has not been adequately challenged. Here we addressed this issue with the aid of a VEGF-based conditional transgenic system in which months-long exposure to VEGF leading to continual elevation of synaptic plasticity and markedly enhanced neurogenesis, eventually culminates in granule cell apoptosis and greatly reduced DG cellularity. This experimental platform of a DG-restricted cellular damage has provided a unique opportunity to follow DG regeneration initiated upon VEGF de-induction. The DG was efficiently re-built with locally generated new neurons (with proper axonal and dendritic growth) and even an extreme cellular deficit of up to 90 percent was fully restored within a period of 12 weeks. Remarkably, impaired DG-dependent memory evident in the distracted DG was fully rectified following regeneration. Together, these results uncovered a yet unappreciated regeneration potential of adult DG neurogenesis.

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Poster

568. Central Nervous System Regeneration

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Topic: A.07. Transplantation and Regeneration

Support: Brain Canada

Title: Genetic lineage tracing of Müller glia-derived progenitors in the mouse retina *in vivo*

Authors: *C. BOUDREAU-PINSONNEAULT[1,3], M. CAYOUETTE[2,3];
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Abstract: The mammalian retina is incapable of regeneration after neuronal cell loss caused by injury or disease, leading to irreversible blindness. In contrast, most fishes and amphibians have the capacity to regenerate their retina through the reprogramming of Müller glia into progenitor-like cells that are able to proliferate and differentiate into all retinal cell types. Recent studies have demonstrated that Müller glia reprogramming is also possible, at least to some extent, in mammals. After artificial retinal injury and injection of growth factors in the mouse eye, some Müller glia re-entered the cell cycle and BrdU-labelled neurons were observed 5 days after growth factor treatment. Although promising, these studies did not provide direct evidence that Müller glia actually generated new neurons, as genetic lineage tracing was not performed. Here we used a Glast-CreERT2;RosaYFP mouse line to study this question *in vivo*. We have shown that the RosaYFP reporter is specifically expressed in adult Müller glia 4 days after 4 intraperitoneal injections of tamoxifen, providing a highly specific and efficient genetic lineage tracing tool. To reprogram the Müller glia in a progenitor state and stimulate proliferation, we injected NMDA and epidermal growth factor (EGF) in the eyes of Glast-CreERT2;RosaYFP mice that were previously injected with tamoxifen. Müller glia-derived progenitors and their descendants will then be followed using expression of the RosaYFP reporter. Results from these ongoing studies will be presented. We next plan to manipulate gene expression in Müller glia-derived progenitors using *in vivo* electroporation of a Cre-inducible expression vector. This work may lead to novel therapies for blindness by promoting endogenous Müller glia to regenerate retinal cell types lost after injury or disease.

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Poster

568. Central Nervous System Regeneration

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Program#/Poster#: 568.08/A51

Topic: A.07. Transplantation and Regeneration

Title: A challenge to induce retinal regeneration in mouse retina

Authors: *Y. BABA, S. WATANABE;
Univ. of Tokyo, Minato-Ku, Japan

Abstract: Backgound: Adult mammalian retina is incapable of regeneration after traumatic injury, which results in retinal degeneration and permanent vision loss. In lower vertebrates, zebrafish retina can be repaired after traumatic injury through Müller glia proliferation and neural differentiation. In contrast, few Müller glia in mouse retina enter the cell cycle after the injury, and several transcription factors, including Ascl1, related with retinal regeneration failed to be expressed in the damaged retina. These findings raise the possibility that transducing transcription factors could fully reprogram Müller glia, allowing Müller glia to proliferate in the mouse retina. To date, I found that Ascl1-NICD3 cotransfection induced cell proliferation of Müller glia in ICR mice retinal explants. Purpose: To reveal the mechanism of Müller glia proliferation by Ascl1-NICD3 and characterize the biological significance of Ascl1-NICD3 inducing proliferation, gain-of-function analysis was performed under various conditions. Results: Gain-of-function analysis using Müller glia specific promoter Hes5 showed that Ascl1-NICD3 induces Müller glia proliferation cell-autonomously *in vitro*. In the marker expression analysis, NICD3 and Ascl1-NICD3 enhanced Nestin expression, and Ascl1-NICD3 induced retinal progenitor cell marker Chx10 expression *in vitro*. In addition, cell proliferation of Müller glia at P9 (n = 3) and P20 (n = 1) was elicited by Ascl1-NICD3 transfection *in vivo*. Furthermore, Ascl1-NICD3 inducing proliferation was occurred in C57/BL6 mice retinal explants which were previously reported to be difficult to induce cell proliferation.

Disclosures: **Y. Baba:** None. **S. Watanabe:** None.

Poster

568. Central Nervous System Regeneration

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 568.09/A52

Topic: A.07. Transplantation and Regeneration

Support: NIH

March of Dimes Foundation - Basil O'Connor award

Klingenstein Foundation Award in Neuroscience

NSF

Shriners Hospital for Children

Title: Hedgehog signaling regulates tissue regeneration in Xenopus laevis tadpoles

Authors: *A. M. HAMILTON[1], L. N. BORODINSKY[2];
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Abstract: Hedgehog signaling regulates tissue regeneration in *Xenopus laevis* tadpoles The Hedgehog signaling pathway regulates a wide variety of biological processes, including cellular proliferation, migration and stem cell differentiation and specification. Recent studies have also demonstrated that enhancing Hedgehog signaling following neural injury improves regeneration in the peripheral and central nervous system. It should be noted, however, that runaway Hedgehog signaling is a common feature in a number of cancers, making it imperative to future therapeutics that the exact mechanisms underlying Hedgehog's pro-regenerative capacity be characterized in detail to allow for targeted clinical manipulation. Using the *Xenopus laevis* tadpole as a model, we find that pharmacological manipulation of the Hedgehog co-receptor Smoothened (Smo) following tail amputation significantly alters regeneration of spinal cord, notochord and muscle in a tissue-specific manner, while perturbing Hedgehog signaling in intact tadpoles does not affect ongoing tissue development. Enhancing Hedgehog signaling by incubating amputated tadpoles with SAG, a Smo agonist, prevents the outgrowth of the spinal cord, whereas muscle regeneration remains normal. In contrast, inhibiting Hedgehog signaling with cyclopamine leads to the outgrowth of a normally elongated spinal cord, whereas muscle regeneration is blocked. Furthermore, we find that perturbing Hedgehog signaling for only the first 24 hours post amputation is sufficient to induce the effects on spinal cord and muscle regeneration observed after 72 full hours of treatment, suggesting that regulation of Hedgehog signaling is critical during the first stages post injury. In addition, we find that within 36 hours of amputation, continuous exposure to SAG or cyclopamine induces increased and decreased numbers of Sox2-positive neural progenitor cells in the regenerating tissue, respectively. These results suggest that a delicate balance of neural progenitor production, migration and differentiation is necessary to achieve successful tissue regeneration, and that Hedgehog plays different roles in the regeneration of different tissues, emphasizing the importance of targeting Hedgehog manipulation in a spatially and temporally restricted fashion. Supported by Basil O'Connor Award - March of Dimes Foundation, Klingenstein Foundation Award in Neuroscience, NSF, NIH-NINDS and Shriners Hospital for Children.

Disclosures: A.M. Hamilton: None. **L.N. Borodinsky:** None.

Poster

568. Central Nervous System Regeneration

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 568.10/A53

Topic: A.07. Transplantation and Regeneration

Support: Greater Milwaukee Foundation, Shaw Scientist Award

Title: CNS regeneration: investigating the transcriptional combinatorial logic underlying successful regeneration in zebrafish

Authors: *A. J. UDVADIA[1], I. VENKATESH[2];
[1]Biol. Sci., Univ. of Wisconsin Milwaukee, Milwaukee, WI; [2]Marquette Univ., Milwaukee, WI

Abstract: CNS injury in adult mammals fails to stimulate a regenerative response and usually results permanent disability. In contrast, CNS injury in fish elicits a robust regenerative response often leading to almost full recovery of function. Since the basic machinery regulating the wiring of the nervous system is well conserved across vertebrate species, the underlying difference stems from the relative abilities to restart the axon growth machinery in response to CNS injury. Our work is focused on discovering the gene regulatory network underlying successful CNS regeneration in zebrafish. We have discovered a combination of three transcription factors from the bZIP and bHLH transcription factor families that are essential for regeneration-associated expression of GAP-43 and successful target reinnervation in a zebrafish optic nerve transection injury model. We are now investing the mechanisms underlying the synergistic activities of this critical combination. One possibility is that they regulate overlapping, but distinct transcriptional networks, which together are necessary for successful regeneration. A second possibility is that they physically and/or functionally act together to regulate a common regeneration-associated gene regulatory network. Our current work investigates protein-protein and protein-gene interactions involving these transcription factors to understand the transcriptional combinatorial logic underlying successful vertebrate CNS regeneration.

Disclosures: **A.J. Udvadia:** None. **I. Venkatesh:** None.

Poster

568. Central Nervous System Regeneration

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 568.11/A54

Topic: A.07. Transplantation and Regeneration

Title: GDNF-secreting Schwann cells in multichannel OPF+ hydrogel scaffolds promote ascending axonal regeneration, remyelination, and partial locomotor recovery following complete spinal cord transection in rats

Authors: *B. K. CHEN, N. N. MADIGAN, J. S. HAKIM, A. M. SCHMEICHEL, A. M. KNIGHT, S. ZHANG, J. J. NESBITT, M. DADSETAN, M. DADSETAN, T. CHIANG, M. J. YASZEMSKI, A. J. WINDEBANK;
Neurol., Mayo Clin. Rochester, Rochester, MN

Abstract: Positively-charged oligo [poly (ethylene glycol) fumarate] (OPF+) is a biodegradable hydrogel with biomechanical properties similar to spinal cord tissue. In this study, OPF+ is used in a combinational tissue engineering approach for the investigation and in the treatment of spinal cord injury. Multichannel OPF+ scaffolds loaded with primary Schwann cells (SCs) or genetically-modified Schwann cells secreting glial cell-derived neurotrophic factor (GDNF-SCs) were implanted into completely transected rat spinal cords at the T9/10 level. GDNF-SCs promoted regeneration of higher numbers of axons (2773.0 ± 396.0, mean ± SEM) into OPF+ scaffolds than primary SCs (1666.0± 352.2) ($p<0.05$) (n=10 animals). A central and ventral midline orientation of axonal growth was observed. The number of neurons projecting caudally through the scaffold was significantly higher in GDNF-SC scaffolds as identified by retrograde fast blue (FB) tracing. The majority of FB-labelled ascending axons were intraspinal motor neurons. GDNF-SC implantation enhanced the remyelination of regenerating axons. The numbers of unmyelinated and myelinated axons, and the percentage of axons that were myelinated were each higher in the GDNF-SC OPF+ group. Myelinating cells in the tissue engineered spinal cord were demonstrated to be Schwann cells from the host animal. p75+ cell density increased in direct proportion to increasing axonal density in SC and GDNF-SC channels with strongly positive correlation coefficients (Pearson $r=0.8995$, $p<0.0001$ in SC channels, and Pearson $r=0.7665$, $p<0.0001$ for GDNF-SC channels). Axons were observed to associate with p75+ cells as premyelinated complexes, and myelinating axon bundles. Transected animals transplanted with GDNF-SC OPF+ scaffolds demonstrated partial hindlimb locomotor recovery at weeks 3 and 4 following surgery.

Disclosures: B.K. Chen: None. **N.N. Madigan:** None. **J.S. Hakim:** None. **A.M. Schmeichel:** None. **A.M. Knight:** None. **S. Zhang:** None. **J.J. Nesbitt:** None. **M. Dadsetan:** None. **M. Dadsetan:** None. **T. Chiang:** None. **M.J. Yaszemski:** None. **A.J. Windebank:** None.

Poster

568. Central Nervous System Regeneration

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Topic: A.07. Transplantation and Regeneration

Support: The Bryon Riesch Paralysis Foundation

SCIS/Unite 2 Fight Paralysis

Title: The tumor suppressor HHEX restricts axon growth in central nervous system neurons

Authors: *M. SIMPSON[1], I. VENKATESH[1], B. CALLIF[1], L. THIEL[1], D. COLEY[1], K. WINSOR[1], Z. WANG[1], J. LERCH[2], M. G. BLACKMORE[1];
[1]Marquette Univ., Milwaukee, WI; [2]The Ctr. for Brain and Spinal Cord Repair, The Ohio State Univ., Columbus, OH

Abstract: Neurons in the peripheral nervous system respond to injury by activating transcriptional programs supportive of axon growth, ultimately resulting in functional recovery. In contrast, neurons in the adult central nervous system (CNS) possess a limited capacity to regenerate axons after injury, fundamentally constraining repair. We and others have shown previously that activating pro-regenerative gene expression in CNS neurons is a promising therapeutic approach, but progress is hampered by incomplete knowledge of the underlying transcription factors. In order to identify novel regulators of axon regeneration, we employed high content assays of neurite outgrowth, testing sixty-nine transcription factors that have been previously associated with cellular growth and motility in non-neuronal systems. This screen revealed two novel transcription factors (E2F1 and YAP1) as growth promoting, and four (PITX1, RBM14, ZBTB16, and HHEX) as growth inhibiting. Follow-up experiments focused on HHEX, the most potent and consistent growth inhibitor. Immunohistochemistry with axon-specific Tau1 antibodies showed that HHEX overexpression in cortical neurons reduced both initial axonogenesis and the rate of axon elongation, and domain deletion analysis strongly implicated transcriptional repression as the underlying mechanism. Although HHEX is unstudied in the CNS, we used immunohistochemistry and western blotting to show that HHEX is widely expressed in CNS neurons, including corticospinal tract neurons after spinal injury. Intriguingly, peripheral neurons lack native HHEX, and forced overexpression of native HHEX restricted axon growth potential in DRG neurons. These findings suggest a role for HHEX in limiting the regenerative capacity of mature CNS neurons.

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Poster

568. Central Nervous System Regeneration

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 568.13/A56

Topic: A.07. Transplantation and Regeneration

Support: NS088943

Title: Strategies to generate migratory precursors for cortical projection neuron replacement

Authors: *M. GRONSKA, H. BELALCAZAR, N. MCKEEHAN, J. HEBERT;
Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract: The human neocortex is subject to many insults such as neurodegeneration to which there is no cure. Previous attempts to replace lost cortical projection neurons failed because the cells did not migrate outside the injection site. We propose an alternative approach where we take advantage of highly migratory medial ganglionic eminence (MGE) cells that have been shown to migrate long distances upon transplantation into the neocortex of rats and mice. Yet, MGEs give rise primarily to inhibitory GABAergic interneurons. Using recent developments in cell reprogramming, we seek to determine the transcription factor and chromatin remodeling factor combinations that would reprogram MGE precursors into cortical projection neurons. We designed a doxycycline inducible system, that allows for a temporal control of gene expression using lentiviruses carrying the genes of interest and Cre recombinase, TRE-GeneX-IRES-Cre. Thus, we will infect embryonic day 12.5 donor mice MGE cells that carry doxycycline responsive Rosa26rtTA and TauloxP-STOP-loxP-mGFP-IRES-LacZ reporter constructs, with various combinations of the lentiviral constructs. We will test for *in vivo* and *in vitro* reprogramming using cell cultures and stereotaxic injections into the adult mouse cortex. Reprogrammed cells will be tested for marker expression and electrophysiological properties. We are currently in the process of screening over 31 possible gene candidates. Our preliminary results suggest that Brn2 and NeuroD genes may be involved in the MGE to cortical projection neuron cell fate conversion.

Disclosures: **M. Gronska:** None. **H. Belalcazar:** None. **N. McKeehan:** None. **J. Hebert:** None.

Poster

568. Central Nervous System Regeneration

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Program#/Poster#: 568.14/A57

Topic: A.07. Transplantation and Regeneration

Support: International Spinal Research Trust

Netherlands Organisation for Scientific Research

Title: Combinatorial expression of transcription factors to promote axon regeneration

Authors: *C. L. ATTWELL[1], N. FAGOE[1], R. E. VAN KESTEREN[2], A. B. SMIT[2], J. VERHAAGEN[1], M. R. J. MASON[1];
[1]Neuroregeneration, Netherlands Inst. For Neurosci., Amsterdam Zuidoost, Netherlands; [2]Dept of Mol. and Cell. Neurobio., Ctr. for Neurogenomics and Cognitive Res., Amsterdam, Netherlands

Abstract: Objective. Dorsal root ganglia (DRG) neurons are ideal for research into the intrinsic regeneration associated gene (RAG) program. Injury to the central projection of these neurons in the spinal cord does not result in regeneration, but after a lesion to the peripheral projection an increase in growth of the central projection is observed. We hypothesised that the RAG program is coordinated by combinations of transcription factors (TFs) that act synergistically or in a complementary fashion. This hypothesis was tested in two approaches: 1. *In vivo* AAV vector-mediated simultaneous overexpression of ATF3, c-Jun, STAT3 and Smad1, four TFs in injured DRG neurons which have been functionally linked to axon regeneration and are known to physically and functionally interact. 2. Promoter analysis of the RAG program which resulted in the identification of nine key TF families, some of which were previously linked to regeneration (AP1, ATF, KLF) and some of which are not (e.g. the MEF family). We systematically screened combinations of these TFs *in vitro*. **Methods**: 1. ATF3 alone or the combination of ATF3, c-Jun, STAT3 and Smad1 were over expressed in the left L4/L5 DRG of rats using an AAV5-dual vector[1,2] that also expresses GFP. The L4, L5 dorsal roots were transected and repaired. Axonal regeneration was assessed histologically and sensory recovery tested functionally. 2. Nine TFs identified by promoter analysis of the RAG program were screened in various combinations in the F11 neuronal cell line with Cellomics neurite length analysis. All single TFs, all possible pairs, and selected combinations of 3 and 4 TFs were tested. **Results**: 1. Over-expression of ATF3 or the combination of ATF3, c-Jun, STAT3 and Smad1 together resulted in faster axonal growth after dorsal root injury, but no additional benefits of the combination over ATF3 alone were observed. No sensory recovery was observed. 2. Of the nine selected TFs screened in F11 cells several combinations of transcription factors promoted synergistic increases in neurite growth, which included combinations of TFs of the ATF, KLF, MEF and STAT families. **Conclusion**: We successfully delivered multiple TFs to DRG neurons *in vivo*. Simultaneous overexpression of four known pro-regenerative TFs promoted faster axon regeneration in the dorsal root *in vivo*, but without apparent synergistic effects. Identification of key TFs by RAG promoter analysis followed by systematic combinatorial screening has yielded several more promising combinations of TFs, which we are currently testing *in vivo* for effects on regeneration

and gene expression. 1.Fagoe et al *Gene Ther*. 2014 Mar;21(3):242-52 2. Mason et al *Mol Ther*. 2010 Apr;18(4):715-24

Disclosures: **C.L. Attwell:** None. **N. Fagoe:** None. **R.E. van Kesteren:** None. **A.B. Smit:** None. **J. Verhaagen:** None. **M.R.J. Mason:** None.

Poster

568. Central Nervous System Regeneration

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 568.15/A58

Topic: A.07. Transplantation and Regeneration

Support: Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

Title: Reestablishment of axonal subdomains in regenerating axons of the optic nerve

Authors: ***M. A. MARIN**[1], S. DE LIMA[2], H.-Y. GILBERT[3], A. MARTINEZ[2], L. BENOWITZ[3], M. RASBAND[1];
[1]Baylor Col. of Med., Houston, TX; [2]Univ. Federal do Rio de Janeiro, Rio de Janeiro, Brazil; [3]Boston Children's Hosp. and Harvard Med. Sch., Boston, MA

Abstract: Myelinated axons are divided into distinct excitable domains, including the axon initial segment (AIS) and nodes of Ranvier. The AIS serves as both a physical barrier between the axonal and somato-dendritic compartments of the neuron and as the site of action potential (AP) initiation. Nodes of Ranvier are responsible for the rapid and efficient propagation of APs along the axon. Disruption of the AIS or nodes of Ranvier by injury or disease has a dramatic impact on neuronal function. Thus, any therapeutic strategy aimed at nervous system repair or regeneration must include the reestablishment or maintenance of these excitable domains. Myelinated axons of the adult mammalian central nervous system are incapable of self-regeneration after injury. However, intravitreal administration of proinflammatory glucans as well as deletion of the PTEN gene in retinal ganglion cells (RGC) after injury to the optic nerve allows for substantial long distance growth of axons. When these treatments are combined with elevation of cAMP, some regenerating axons can grow past the optic chiasm and reinnervate the dorsal lateral geniculate, suprachiasmatic nucleus, and other central target areas. Using this model, we performed a detailed analysis of the dismantling and reorganization of the AIS and nodes of Ranvier. In the absence of any treatment, immunofluorescence reveals a dismantling of the excitable domains within 48 hours of the crush. Loss of nodes of Ranvier is detectable by 6 hours after crush in the immediate vicinity of the crush site, and across the entire optic nerve

within a week of the crush. Analysis of the PTEN$^{f/f}$+Zymosan+cAMP regeneration model by both immunofluorescence and electron microscopy (EM) demonstrates the reestablishment of excitable domains and remyelination of regenerating axons in the optic nerve. Analysis by immunofluorescence revealed the reestablishment of RGC-AIS in the retina 6 weeks after crush. We also observed growth of axons and reestablishment of nodes of Ranvier proximal, distal and within the crush site of the optic nerve 6-12 weeks after crush. Furthermore, EM analysis of regions close to the chiasm shows remyelination of regenerating axons 12 weeks after lesion. Thus, regenerating axons are capable of reestablishing excitable domains and undergoing remyelination, supporting the possibility of efficient signal conduction.

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Poster

568. Central Nervous System Regeneration

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Topic: A.07. Transplantation and Regeneration

Support: Grant-in-Aid for JSPS Fellows 25-5321

JSPS KAKENHI Grant 26430043

Waseda University Grant for Special Research Projects 2013B-171

Title: Dephosphorylation of CRMP2 enhances recovery after spinal cord injury

Authors: *J. NAGAI[1], Y. KITAMURA[1], K. OWADA[1], Y. GOSHIMA[2], T. OHSHIMA[1]; [1]Waseda Univ., Tokyo, Japan; [2]Yokohama City Univ., Yokohama, Japan

Abstract: The presence of inhibitory molecules and the lack of neurotrophic factor are two major difficulties to central nervous system (CNS) regeneration. Common mediator of these two has been not found yet. Collapsin response mediator protein 2 (CRMP2) was originally identified as a mediator of Semaphorin3A-induced repulsive response. CRMP2 directly binds and stabilizes cytoskeletal microtubule polymerization and transport tyrosine kinase B (TrkB) to axonal tip, the receptor for brain-derived neurotrophic factor (BDNF), to promote axonal elongation. Meanwhile, inhibitory molecules-induced signals phosphorylate CRMP2 to decrease its affinity to cytoskeleton proteins, leading to axonal growth inhibition. However, the role of CRMP2 phosphorylation after CNS injury *in vivo* remains unknown. Here we investigate the role

of CRMP2 phosphorylation after spinal cord injury (SCI) using CRMP2 knock-in (KI) mouse where CRMP2 phosphorylations by Cdk5 and GSK3beta are eliminated by replacing serine522 with alanine residue. Elevated level of pCRMP2 was observed in injured spinal cord. Inhibition of CRMP2 phosphorylation exhibited neuroprotective effect against SCI by suppressing depolymerization of microtubules and fibrous scar formation. This permissive environment for enhanced axon growth of 5-HT-positive raphe-spinal tract induced locomotor recovery in CRMP2KI mice. To examine the signaling cascades involving CRMP2 phosphorylation, we cultured dorsal root ganglion (DRG) neurons. Suppressed axonal growth inhibition by chondroitin sulfate proteoglycan (CSPG) and enhanced axonal elongation with BDNF were observed in CRMP2KI neurons. Therefore, dephosphorylation of CRMP2 could be a unique approach to repair injured CNS by reduced inhibitory responses and enhanced sensitivity to neurotrophin.

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Poster

568. Central Nervous System Regeneration

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 568.17/A60

Topic: A.07. Transplantation and Regeneration

Title: A role of autophagy in microtubule assembly and axon regeneration

Authors: ***M. HE**, Y. DING, Z.-G. LUO;
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Abstract: Limited axon regeneration after spinal cord injury (SCI) results in lots of structural and functional deficits. Minimal intrinsic axon growth capacity and extracellular inhibitory factors are major obstacles for spinal cord repair. Before a lesioned axon attempts to pass through the inhibitory environment, the primary and crucial step is to assemble a new growth cone. However, mammalian CNS axons after injury usually form retraction bulbs, which impede the growth cone re-assembly. Microtubule stabilization prevents the formation of retraction bulbs and promotes axon regeneration. Here, we report a novel role of autophagy in neuronal microtubule assembly and axon regeneration. We found that treatment of cultured rat cortical neurons with a membrane-permeable peptide TAT-Beclin, which was used to specifically induce autophagy, increased microtubule stability and promoted its bundling. Furthermore, TAT-Beclin-enhanced microtubule stability was through specific degradation of a microtubule destabilizing

protein SCG10. Interestingly, TAT-Beclin treatment dampened the inhibitory effect of myelin on cultured neurons, and prevented the formation of retraction bulbs during axon degeneration after injury in cultured neurons and sensory neurons in spinal cord. Finally, application of TAT-Beclin attenuated axon retraction of corticospinal tract in mice subjected to dorsal spinal cord hemi-section and promoted its locomotor function recovery. This study indicates a potential role of manipulation of autophagy activity in axon regeneration after injury.

Disclosures: **M. He:** None. **Y. Ding:** None. **Z. Luo:** None.

Poster

568. Central Nervous System Regeneration

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Topic: A.07. Transplantation and Regeneration

Support: The Bryon Riesch foundation

SCIS/U2FP

Title: Epigenetic profiling reveals a developmental decrease in promoter accessibility of regeneration associated genes in CNS neurons

Authors: *I. VENKATESH, M. SIMPSON, B. CALLIF, M. BLACKMORE;
Dept. of Biomed. Sci., Marquette Univ., Milwaukee, WI

Abstract: Embryonic neurons and peripheral neurons respond to axonal injury with activation of transcriptional programs conducive to regrowth. In contrast, mature CNS neurons fail to reactivate expression of crucial regeneration associated genes (RAGs) in response to injury, resulting in failed axon growth and permanent loss of function. Forced re-expression of key RAGs in mature CNS neurons is a promising strategy for therapeutic intervention. We and others have previously shown that ectopic expression of pro-regenerative factors such as KLF7 and Sox11 promotes axon regeneration in CNS neurons. Growth is incomplete however hinting that additional factors limit the cell intrinsic ability to promote growth. One reason could be restricted DNA accessibility due to a closed chromatin conformation in genomic loci corresponding to key RAGs in CNS neurons. We hypothesized that the developmental decline in regenerative ability is accompanied by a corresponding decrease in RAG promoter accessibility for pro-regenerative transcription factors. To test this, we profiled the epigenetic landscape surrounding promoters of select RAGs across development for changes in histone modifications indicative of DNA

accessibility. We observed that RAGs including KLF7, Sox11, cJUN and GAP-43 switch from a relaxed chromatin environment to a restricted chromatin state as CNS neurons age. We are currently combining pro-regenerative TFs along with treatments that relax chromatin in assays of axon outgrowth. Overall, understanding changes in the chromatin landscape as CNS neurons mature, opens up the possibility of manipulating epigenetic modifications to promote axon outgrowth after injury.

Disclosures: I. Venkatesh: None. **M. Simpson:** None. **B. Callif:** None. **M. Blackmore:** None.

Poster

568. Central Nervous System Regeneration

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: A.07. Transplantation and Regeneration

Support: Gertrud-Reemtsma Foundation

Title: Human ES cell- and iPS cell-derived astrocytic subtypes for transplantation after spinal cord injury

Authors: *I. K. SIMEONOVA[1], B. SANDNER[2], M. MOTSCH[2], T. SCHACKEL[2], I. GOGANAU[2], S. LIU[2], B. WINNER[3], A. BLESCH[2];
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Abstract: Grafting of induced pluripotent stem cells (iPSCs)-derived NPCs has shown promise in promoting functional recovery in animal models of spinal cord injury (SCI), but the contribution of different neuronal and glial cell populations to morphological and functional improvements remains poorly understood. To better define the role of astrocytic subtypes, we have generated patterned NPCs and glia with specific phenotypes from human embryonic stem cells (ESCs) and iPSCs. Caudalized pure astrocytic lines were generated following standard neural induction protocols, followed by a long expansion phase of neurospheres in low attachment conditions. Prior to terminal differentiation, dissociated neurospheres cultivated on poly-L-ornithin/laminin consist of a homogeneous population of vimentin-expressing precursors, resembling early spinal glial progenitors present during CNS development. The characteristics of maturing, differentially patterned human ESC- and iPSC-derived astrocytes were examined *in vitro* and their pro-regenerative capacity *in vivo*. Terminal differentiation was induced by

treatment with BMPs, FGF1, CNTF or mere growth factor withdrawal for at least 2 weeks. While no obvious differences could be observed between the latter two groups, BMP-treated astrocytes were up to ten times larger and had larger nuclei, whereas FGF1-treated astrocytes displayed a smaller cell size. These differences were maintained after withdrawal of BMPs, FGF1 or CNTF and a 2-week exposure to pro-inflammatory factors.This indicates that functional differences might exist between differentiation groups, which might be maintained in a pro-inflammatory lesion-environment. We are currently analyzing the effect of specific astrocytic lines on neurite growth in co-cultures of rat primary DRG neurons on maturing astrocytes and potential mechanisms underlying these effects. In ongoing studies, cells have been grafted into the lesioned rat spinal cord to investigate *in vivo* differentiation, integration and host-graft interaction. Based on *in vitro* and *in vivo* data, we aim to determine whether iPS-derived glial progenitor cells integrate into the host spinal cord to form a conducive substrate for axonal growth and whether pre-differentiation can influence these process.

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Poster

568. Central Nervous System Regeneration

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Program#/Poster#: 568.20/A63

Topic: A.07. Transplantation and Regeneration

Support: International Spinal Research Trust

Title: Peripheral electrical stimulation to enhance the regenerative capacity of sensory axons after spinal cord injury

Authors: *I. GOGANAU[1], B. SANDNER[2], K. FOUAD[3], A. BLESCH[2];
[1]Neuroregeneration, Universitats Klinikum Heidelberg, Heidelberg, Germany; [2]Spinal Cord Injury Ctr., Heidelberg Univ. Hosp., Heidelberg, Germany; [3]Fac. of Rehabil. Med., Univ. of Alberta, Edmonton, AB, Canada

Abstract: Axotomy of peripheral nerves induces complex changes in gene expression of dorsal root ganglion (DRG) neurons contributing to successful regeneration after PNS or subsequent spinal cord lesions. We hypothesized that evoked neuronal activity by direct peripheral electrical stimulation (ES) can enhance regeneration-associated gene (RAG) expression in DRG neurons and support the growth of the central spinal cord branch. For ES, temporary or chronic, bipolar

cuff electrodes were placed around the sciatic nerve at mid-thigh level in adult female Fischer 344 rats. Sham animals received cuff electrodes, but no stimulation for the same duration; naïve animals and animals with PNS lesions served as additional controls. Basic ES parameters were 20Hz, 0.2ms square pulse, 5V with an intensity of 2x motor threshold. 7 days (7d) after cuff placement, DRG neurons were isolated, cultivated, and neurite length was quantified using ImageJ. Short ES for 1h enhanced neurite growth of DRG neurons isolated 7d post-stimulation and cultivated on 5µg/ml laminin, increasing the average longest neurite by 104% compared to naïve and sham animals (ANOVA $p<0.0001$; PLSD $p<0.01$), while CL increased growth by 382%. When DRGs were isolated 1 day after ES, no effect on neurite growth was observed. Repeated ES for 7d (1h/d) also increased the growth compared to sham animals ($p<0.01$), but no more than a single 1 h stimulation. However, a single ES applied for an increased duration (7h) seems to further increase the neurite growth-promoting effect compared to sham animals. Similar findings were obtained on less permissive substrate (0.5µg/ml laminin). The pattern of growth and the timeline were similar to a PNS lesion, suggesting a partial overlap in mechanisms. Current experiments analyze the expression of RAGs in DRGs, and dorsal column sensory axon regeneration *in vivo* after ES. Taken together, our results indicate that the growth capacity of DRG neurons can be modulated *in vivo* by externally-induced activity providing a therapeutic strategy to increase sensory axon regeneration in the injured spinal cord.

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Poster

568. Central Nervous System Regeneration

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 568.21/A64

Topic: A.07. Transplantation and Regeneration

Support: NEI Grant R01-EY020297

NINDS Grant F31-NS087789-01A1

Title: The role of mitochondrial dynamics in CNS axon regeneration

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Abstract: Central nervous system (CNS) disease or injury is often accompanied by progressive axon degeneration, leading to lost sensory, motor, or cognitive abilities. In search of factors to restore degenerated CNS axons, we identified a group of developmentally regulated transcription factors, the Krüppel-like transcription factors (KLFs), which differentially suppress or enhance retinal ganglion cell (RGC) axon growth. However, the downstream mechanisms by which KLFs regulate axon growth are unknown. Evidence suggests one downstream effector may be mitochondrial (Mt) fission/fusion dynamics. We recently showed that suppressing fission (increasing fusion) leads to a loss in RGC axon growth inhibition by chondroitin sulfate proteoglycans, presenting evidence of mechanism in which CNS axon growth and guidance responses can be regulated by Mt fission-fusion. Moreover, suggesting that suppressing fission is a potential therapeutic strategy for improving axon regeneration after CNS trauma. To identify whether Mt fission/fusion mechanisms also underlie the axon suppressing/enhancing activity of KLFs, we are investigating the potential ability for KLFs to critically regulate Mt genes. Pertinent to our previous findings, we found that axon growth suppressing KLFs increase the genetic expression of mitochondrial fission process 1,18 kDa (MTP18), a positive regulator of Mt fission, supporting the hypothesis that increased fission is inhibitory for axon growth in RGCs. We hypothesize that KLF-mediated regulation of the mitochondrial dynamics, in part through MTP18 expression, regulates intrinsic axon growth ability in CNS neurons. The overall goal is to improve our understanding of how Mt fission/fusion regulates axon regeneration and to use this understanding to identify strategies for restoring axon growth after CNS injury or disease.

Disclosures: **A. Kreymerman:** None. **M.B. Steketee:** None. **J.L. Goldberg:** None.

Poster

568. Central Nervous System Regeneration

Location: Hall A

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Topic: A.07. Transplantation and Regeneration

Support: NCGR INBRE sequencing and bioinformatics pilot award

NSF grant IOS-1353123

Title: Whole transcriptome response to spinal injury in the regenerating spinal cord of the opossum, Monodelphis domestica

Authors: *B. J. WHEATON[1], P. UMALE[2], A. SUNDARARAJAN[2], S. GUIDA[2], J. SENA[2], F. SCHILKEY[2], K. M. DZIEGIELEWSKA[3], N. R. SAUNDERS[3], R. D. MILLER[1];
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Abstract: When the spinal cord is injured during early development the axons have the capacity to grow across the injury site and form functional circuitry. As the spinal cord matures this ability is lost. This has been demonstrated extensively using the Grey short-tailed opossum, *Monodelphis domestica,* a South American marsupial whose young are born at an altricial stage of neural development. In these animals there is a pronounced growth of axons across an injury made at post-natal-day (P) 7, but no such regrowth following an injury at P28. The mechanisms underlying the increased regeneration of the immature cord and those controlling the switch to the non-regenerative state are not fully understood. Here we have investigated this by analyzing the spinal cord transcriptome as it responds to injury over time. Opossum spinal cords were completely transected in the mid-thoracic region at either P7 or P28; cords were collected for analysis after 1, 3 or 7 days. RNA was extracted from the segment of tissue containing the injury site (or equivalent areas from controls), processed for high throughput Illumina RNA sequencing and differentially expressed genes were identified between selected samples using standard algorithms. Two analyses were performed: Developmental analysis of control cords between the permissive and nonpermissive ages and injury progression analysis studying the time course of the response to injury. Several development-regulating genes were more highly expressed in the P7 animals. We found higher expression of homeodomain genes orthopedia homeobox (*Otp*) and ISL LIM homeobox genes (*Isl1*), which are involved in CNS and motor neuron development, respectively. Also higher at this age were the POU class 4 homeobox (*Pou4f1*), which is important in the developing sensory nervous system and the cadherin *Celsr3* which is involved in axon guidance. In the P28 animals several genes involved in axonal support were more highly expressed including myelin-associated genes myelin basic protein (*Mbp*), myelin-associated glycoprotein (*Mag*), myelin oligodendrocyte glycoprotein (*Mog*), oligodendroctye-lineage factor-1 & 2 (*Olig1 & 2*) along with glial fibrillary acidic protein (*Gfap*). Immune related genes including *Cd74, Cd200*, interleukin 1 receptor accessory protein (*Il1rap*) and chemokine ligand 14 (*Cxcl14*) were also more highly expressed at P28. The developmental state of the spinal cord changes considerably as it matures between the ages when axonal regrowth occurs and when it does not. Understanding how this changing internal environment affects the outcome after injury may be an important step in explaining the regenerative response.

Disclosures: B.J. Wheaton: None. **P. Umale:** None. **A. Sundararajan:** None. **S. Guida:** None. **J. Sena:** None. **F. Schilkey:** None. **K.M. Dziegielewska:** None. **N.R. Saunders:** None. **R.D. Miller:** None.

Poster

568. Central Nervous System Regeneration

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 568.23/A66

Topic: A.07. Transplantation and Regeneration

Title: LPA pathway modulates intrinsic axon growth of intact CNS neurons after spinal cord injury

Authors: *K. FINK, S. STRITTMATTER, W. CAFFERTY;
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Abstract: Axons fail to regenerate in the adult central nervous system (CNS) after spinal cord injury (SCI) due to decreased growth capacity of adult neurons and an inhibitory growth environment. Myelin associated inhibitors (MAIs) prevent axon growth in the CNS by signaling through the neuronally expressed Nogo receptors (NgR) and PirB. Genetic and pharmacological targeting of the MAI axis modestly increases regeneration of damaged axons yet incompletely restores function after SCI. An additional strategy to enhance recovery would be to form *de novo* circuits through intact axons spared by lesion. Previous work from our laboratory has shown that after unilateral corticospinal tract (CST) injury (unilateral pyramidotomy, uPyX) the intact CST functionally sprouts into denervated spinal cord. After bilateral PyX a *de novo* intact functional circuit emerges between the red nucleus and the nucleus raphe magnus. Furthermore, plasticity within these intact circuits was significantly enhanced in nogo receptor-1 knockout mice (*ngr1-/-*). We sought to identify the mechanism underlying functional sprouting in intact neurons. To this end, we completed uPyX in μ-crystallin-GFP (expresses GFP in CST neurons) wild type (n=6) and *ngr1-/-* (n=6) mice. Two weeks post lesion mice received contralateral intraspinal injections of the retrograde tracer fast blue to label axons that had sprouted across the midline. Two weeks later mice were prepared for laser capture microdissection (LCM) and processed for RNAseq. Transcriptional analysis revealed 1174 genes were significantly differentially expressed between intact sprouting CST neurons and intact non-sprouting CST neurons. Ingenuity Pathway analysis revealed that a number of differentially expressed genes were enriched in the lysophosphatidic acid (LPA) pathway. Significantly, pro-growth genes were up regulated in sprouting neurons with simultaneous down regulation of growth inhibitors in the LPA pathway including LPA receptor 1 (*lpar1)*. Overexpressing the pro-growth genes in cortical neurons *in vitro* resulted in an increase in acute neurite outgrowth as well an increase in axon growth in an *in vitro* injury model. The role of the LPA pathway in modulating functional sprouting of intact neurons after SCI is underway using pharmacological inhibition of lpar1. Wild type mice have undergone unilateral PyX (n=24) or sham lesion (n=24) followed by 10 day treatment of either vehicle (n=12) or lpar1 inhibitor (n=12). Behavior is being assessed using the forelimb pellet retrieval

task and sprouting will be assessed histologically to determine if lpar1 inhibition results in an increase in functional recovery and sprouting after SCI.

Disclosures: **K. Fink:** None. **S. Strittmatter:** None. **W. Cafferty:** None.

Poster

568. Central Nervous System Regeneration

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 568.24/A67

Topic: A.07. Transplantation and Regeneration

Support: UW Dept of Neurosurgery Startup Funds

Title: Biomimetic injectable 3D hydrogels with aligned topography for neural tissue engineering

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Abstract: Hydrogels are soft materials with high water content that are widely used as scaffolds to interface with soft central nervous system tissue. Spinal cord trauma leads to destruction of a highly organized cytoarchitecture that carries information up and down the spinal column. Experimental therapeutic efforts aim to provide aligned topography to support anisotropic regeneration. Although a number of techniques have been developed for producing topography, current methods require complex methodology, and hence it remains challenging to introduce topography within soft 3D hydrogels with ease. Here we describe a simple and reproducible system that results in consistently aligned profiles within 3D matrices using thermally gelling biomimetic polymers that are biocompatible with neuronal cells. A collagen type I (Col)-based thermally gelling hydrogel system was used in combination with other native extracellular matrix proteins: laminin I (LN), hyaluronic acid (HA). Gelling kinetics for all gel types (Col, Col/LN, Col/HA) were examined. Alignment of fibers was obtained by aspirating gelled samples through different syringe gauges. The resulting hydrogels were dried and examined using scanning electron microscopy (SEM). Primary embryonic cell cultures (cortical neurons, spinal motor neurons and spinal interneurons) were first encapsulated in 3D hydrogel solutions, allowed to form gels, and then aligned. Samples were cultured for up to 14d *in vitro* and the resulting samples were fixed and examined using immunohistochemistry. Stained samples were examined and photomicrographs were obtained using an Olympus FV1000 MPE BX61 multi-photon laser. All three combinations of polymer formed consistent gels at 37°C. Col and Col/HA were faster to gel (20 - 22 min, n = 8 - 9 per gel type), while Col/LN took longer (26 - 28 min, n = 8). SEM

images confirmed successful alignment in all gel types using the aspiration and ejection method. We infer from the size of the fibers that the aligned fibers were collagen fibers (~250 nm in diameter). Next, we encapsulated all three neuron types (cortical, spinal motor and spinal interneurons) within the hydrogels and aligned. We found that the cells within the hydrogels survived, differentiated and neurons produced processes along the same direction as the aligned fibrils within the hydrogel. Our data indicate that thermally gelling biomimetic polymers can produce aligned matrices by aspiration and ejection method. This process and material are compatible with the survival of neuronal cells *in vitro* and may be a useful novel platform for regenerative therapies in the Central and Peripheral Nervous Systems.

Disclosures: C.P. Hofstetter: None. **L.J. Kobelt:** None. **L.N. Cates:** None. **Z.Z. Khaing:** None.

Poster

568. Central Nervous System Regeneration

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Topic: A.07. Transplantation and Regeneration

Support: Morton Cure Paralysis Fund

Hermann Foundation

Marine Biological Laboratory

Title: A single cell approach to defining the molecular recipe for successful regeneration of CNS neurons after spinal cord injury

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Abstract: Spinal cord injury (SCI) elicits differential responses in injured neurons: some neurons die, while others survive and regenerate their axons. This phenomenon has been observed in vertebrates ranging from lampreys to mammals. Thus, there is a growing interest in identifying the key intrinsic factors that govern whether or not an injured neuron will regenerate.

Manipulations of single factors often improve axon regeneration, but the effects are modest or incomplete, suggesting that successful regeneration is driven by a more complex set of factors. To address this, we are using an unbiased single cell transcriptome approach, which is a powerful method for identifying the complete molecular profiles and gene networks that drive successful regeneration. This approach is not possible in most SCI models, because it is difficult to reliably distinguish neurons that regenerate from those that do not. Therefore, we are utilizing the lamprey giant reticulospinal (RS) neurons, because they are large, identifiable, and have known and varying regenerative capacities. After spinal cord transection, a reproducible subset of RS neurons survives and regenerates, while another subset dies and fails to regenerate (i.e. "good" and "poor" regenerators). Here, we describe our initial analyses of single cell transcriptome data for several RS neurons, including good and poor regenerators. Neurons were isolated using laser capture microdissection. cDNA libraries were sequenced using RNA-Seq. Resulting reads were mapped to the lamprey genome and quantified using RNA-Seq by Expectation Maximization. A Gene Ontology (GO) analysis of transcripts expressed in the uninjured neurons revealed that the good regenerator differentially expressed genes involved in axon guidance, regulation of intracellular protein transport, Golgi vesicle transport, and regulators of Wnt signaling, suggesting that regeneration-competent neurons express molecular profiles that selectively advantage them for growth even before injury. We then compared the transcriptomes of a poor regenerator before and at 3 days post injury. GO analysis revealed a significant upregulation of genes involved in glutamate receptor activity and calcium channel activity, while genes involved in axon guidance and microtubule-based processes were downregulated, suggesting that excitotoxicity and reduced axon growth contribute to a non-regenerative outcome. Taken together, this pilot study establishes the lamprey RS neurons as a robust model for identifying the complete set of intrinsic factors associated with successful regeneration of CNS axons after spinal injury.

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Poster

568. Central Nervous System Regeneration

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Support: Rosetrees Trust Grant M193

American Association of Anatomists Visiting Scholarship

IRP/IFP Grant P117

Title: PTEN deletion and alpha9 integrin expression enhance adult corticospinal tract regeneration

Authors: *M. R. ANDREWS[1], K. ZUKOR[2], S. MORRIS[1], Z. HE[2], J. W. FAWCETT[3]; [1]Univ. of St Andrews, St Andrews, United Kingdom; [2]F. M. Kirby Program in Neuroscience, Children's Hosp. Boston, Harvard Med. Sch., Boston, MA; [3]Dept. of Clin. Neurosciences, Ctr. for Brain Repair, Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Central nervous system (CNS) axons do not regenerate after injury although several experimental treatments have shown promise for nervous system repair. Contributing to the strong inhibition of regrowth is the extracellular matrix glycoprotein, tenascin-C, which is highly expressed after CNS injury without concomitant neuronal expression of its receptor, alpha9 integrin. To address this issue, we have previously demonstrated that reintroduction of the alpha9 integrin receptor promotes axonal regeneration after dorsal rhizotomy or dorsal column crush lesion to modest levels *in vivo*. Further ongoing studies have suggested that there is a defect in axonal localisation and transport of these integrins within the adult corticospinal tract (CST) using virally-expressed integrins in the CNS. This defect is not present in systems with a greater propensity for regeneration such as in the neonatal corticospinal tract, or in the peripheral nerve. From another perspective on CNS repair, studies evaluating the effects of either conditional deletion or suppression of the phosphatase and tensin homolog (Pten) gene have demonstrated significant levels of axonal regeneration in the CST and optic nerve. These studies showed an upregulation of mTOR (mammalian target of rapamycin) activity as a result of Pten deletion, generating an increased regenerative ability within the CNS. We therefore combined these two therapies of enhancing neuroprotection and intrinsic regenerative capacity by Pten deletion while promoting axonal growth with alpha9 integrin expression and assessed CST regeneration following a T8 spinal cord crush lesion in adult mice. We hypothesize these two therapies will promote significant levels of regeneration in the adult CST further than either treatment alone. Experiments consisted of conditional deletion of Pten in corticospinal neurons at birth and injection of AAV-alpha9integrin-V5 into corticospinal neurons at 8 weeks of age concurrent with spinal cord injury. CST regeneration was anatomically assessed by anterograde tracing with biotinylated dextran amine at 8 weeks post-injury. Our results suggest a strong combinatorial effect on CST axon regrowth following Pten deletion and overexpression of alpha9 integrin in corticospinal neurons.

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Poster

568. Central Nervous System Regeneration

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Support: NRF-2012R1A2A2A01013143

NRF-2012R1A5A2051429

Title: Demethylation of c-Myc gene triggers transcription of a group of regeneration-associated genes in DRG sensory neurons following conditioning peripheral nerve injury

Authors: *H. SHIN[1,2], K. KIM[3], M. KWON[2], B. KIM[2,4];
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Abstract: Conditioning injury (CI) to the peripheral branches of DRG sensory neurons can lead to robust upregulation of many regeneration-associated genes (RAGs), allowing axon regeneration of central branches beyond lesion site in the spinal cord. How the peripheral nerve injury can lead to the coordinated upregulation of RAGs is not fully understood. The current study was designed to examine changes in DNA methylation of RAGs after CI. Although CI induced DNA methylation changes in almost 10% of all genes, the majority of RAGs did not show significant changes in methylation level. Instead, we found methylation changes in several of the transcription factor genes that have known interactions with promoters of RAGs on the basis of bioinformatics analysis. Of these, we focused on c-Myc transcription factor of which demethylation was nicely correlated with increased mRNA expression. Chromatin immunoprecipitation assay showed increased binding of c-Myc after CI to the promoters of a group of RAGs such as c-Jun, Atf3, and Sprr1a, but not to those of Gap43, Npy, and Galanin. Demethylation of c-Myc was observed as early as 4 hours after CI, when apparent mRNA upregulation of the c-Myc-binding RAGs was not found. AAV-mediated overexpression of c-Myc resulted in an increase in the extent of c-Myc occupancy on the promoters of c-Jun, Atf3, and Sprr1a. Intraganglionic injection of AAV5-c-Myc enhanced neurite outgrowth compared to control AAV5-GFP injection when DRGs were freshly dissected and cultured on permissive substrate 4 weeks after injection. These results suggest that DNA methylation of c-Myc precedes and triggers transcription of a group of crucial RAGs for intrinsic regeneration capacity. Further studies will provide novel insights into upstream orchestration of the coordinated transcriptional activation of RAGs in DRG neurons following conditioning peripheral nerve injury.

Disclosures: **H. Shin:** None. **K. Kim:** None. **M. Kwon:** None. **B. Kim:** None.

Poster

568. Central Nervous System Regeneration

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CONACyT Grant 219847

CONACyT Scolarship 243334

Title: DNA methylation as a possible epigenetic barrier preventing Müller glia damage-induced dedifferentiation in mammals

Authors: *L. I. REYES-AGUIRRE[1], M. LAMAS[2];
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Abstract: In response to retinal injury, Müller Glia (MG) can start a gliosis process or dedifferentiate, proliferate and replace dead neurons. This regenerative response occurs naturally in teleost fish but is absent in mammals, despite structural and functional similarities between their retinal cells. In past studies, we have been able to induce MG dedifferentiation in mammals. However, most cells fail to completely lose their glial phenotype and are unable to express photoreceptor markers after being treated with previously tested differentiation protocols. One, or several, kinetic barriers affecting all cells might explain this partial dedifferentiation. Epigenetic memory has been reported as one of such barriers, and is considered responsible for low efficiency in dedifferentiation studies. In order to understand its role on MG response to damage in mammals and to compare it with available information in fish, we analysed early gene expression in mice retina after NMDA-induced damage. Stem-related gene expression was analysed in samples extracted 4, 12, 18 and 24 hours post retinal injury (pi). Real-time PCR revealed a rapid induction of Oct4 and Nanog, which reached its peak at 18h pi. However, these genes were barely detectable shortly after (24h pi). This transient expression suggests a silencing mechanism preserving MG differentiated state. Thus, we analysed the expression of maintenance and *de novo* DNA-methyltransferases (DNMTs), as well as demethylation-related Tet proteins (1, 2, 3), and Gadd45 (a, b). At 4 and 12h pi, we observed a reduction in DNMT3b expression,

accompanied by an increase in Gadd45b relative level. This coincides with the Oct4 and Nanog expression peak, and indicates that an indirect demethylation process allows their transcription. DNMTs levels are restored after this temporal window. These results suggest that DNA methylation acts as an epigenetic memory mechanism and prevents further expression of Oct4 and Nanog, which have been described as necessary for an adequate regenerative response.

Disclosures: L.I. Reyes-Aguirre: None. **M. Lamas:** None.

Poster

569. Adolescent Development: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 569.01/A72

Topic: A.09. Adolescent Development

Support: Center for Nutrition, Learning, and Memory

Abbott Nutrition

Title: Novel mouse models for elucidating the impact of alpha-tocopherol stereoisomers on neonatal brain development

Authors: *J. G. MUN[1], K. DU[1], C. RENDEIRO[1], D. S. MILLER[1], M. BARKER[1], P. KOZAK[1], T. BHATTACHARYA[1], S. RUBAKHIN[1], C.-S. LAI[2], K. MATTHEW[2], J. S. RHODES[1]; [1]Univ. of Illinois, Urbana, IL; [2]Abbott Nutr., Columbus, OH

Abstract: Vitamin E, as α-tocopherol, has long been touted as an antioxidant despite clear evidence for a role in embryogenesis and the maintenance of pregnancy in tocopherol-deficient animal models. Moreover, preferential sequestration of the RRR- stereoisomer of α-tocopherol by tissues including the brain, and recent evidence suggesting translocation into the nucleus of cells suggests that a specific, yet unknown function may exist. Uncovering a specific role for this stereoisomer has been met with the major obstacles of depleting vitamin E from tissues and discriminating the RRR- form from the other 7 stereoisomers. In the current work, we will present two models that address these challenges for studying α-tocopherol in neonatal brain development. In the first study, we paired 24 C57BL/6J mice to produce litters and assigned each pair to one of three AIN-93G-based diets, two of which were α-tocopherol deficient (32 IU RRR-α-tocopherol and 32 IU all-rac-α-tocopherol) and one that was α-tocopherol-adequate (75 IU all-rac-α-tocopherol) as a control. Pup body weights were recorded and on postnatal day 21 (PN21), pups were perfused with saline, tissue weights were recorded, half brains were stored in

paraformaldehyde for histological measures and the other halves were stored at -80 C for biochemical analyses. In the second study, we cross-fostered C57BL/6J pups (N=23) at birth with tocopherol transfer protein-knock out (TTP-/-) mouse dams fed a tocopherol-stripped diet. Mouse milk was shown to be deficient in α-tocopherol and pups within each litter were orally-supplemented daily for 21 days with either RRR-α-tocopherol (0.0010 IU/g body weight), all-rac-α-tocopherol (a synthetic mixture of 8 α-tocopherol stereoisomers; 0.0010 IU/g body weight), or medium chain triglycerides as a vehicle. Pups were perfused on PN21, tissue weights were recorded, and then stored as previously described. Pups from dams fed tocopherol-deficient diets were shown to have significantly reduced body, brain, and liver weights compared to control-fed dams and the 32 IU RRR- treatment showed protection against tissue weight loss compared to the all-rac-α-tocopherol treatment. Biochemical analyses showed that the neonatal brain discriminates between natural and synthetic forms of vitamin E. Furthermore, these methodologies have allowed us to demonstrate proof-of-concept that α-tocopherol stereoisomer profiles and concentrations in the neonatal brain could be feasibly manipulated through oral-supplementation of different vitamin E sources and that α-tocopherol stereoisomer source can significantly alter gross anatomy in the neonate.

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Poster

569. Adolescent Development: Animal Models

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Topic: A.09. Adolescent Development

Support: NIGMS SC2GM109811

Title: Witnessing social defeat stress mediates a depression-like phenotype in female c57BL/6 mice

Authors: F. J. FLORES-RAMIREZ[1], L. M. RIGGS[1], J. B. ALIPIO[1], M. A. HERNANDEZ[1], B. CRUZ[1], S. H. BRAREN[2], P. A. SERRANO[2], *S. D. INIGUEZ[3,1];
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Abstract: Stress exposure is a prevailing risk factor for the development of mood-related illnesses, wherein women represent the majority of those afflicted with depression-, anxiety-, and posttraumatic stress disorder. Despite the growing literature suggesting that affective disorders can arise after a traumatic event is vicariously experienced, this relationship remains to be examined in females at the preclinical level. Thus, the objective of the current investigation is to assess whether the witness defeat stress (WDS) behavioral paradigm (Biol Psychiatry, 73[1], 7-14; 2013) - a model that dissociates emotional versus physical stress - induces a depression-like phenotype in female c57BL/6 mice. To do this, female mice witnessed the social defeat bout of a male conspecific, by a larger CD1 aggressor, for 10 consecutive days. Twenty-four hr after the last stress exposure, mice were tested in the social interaction, sucrose preference, and tail suspension tests. Our results show that when compared to non-stressed controls, female mice exposed to WDS display depressive-like behaviors, as inferred from decreases in social behavior, decreased sucrose preference, and increased immobility in the tail suspension test. Collectively, our data suggests that the WDS paradigm may be used to examine the etiology of vicarious stress-induced mood-related disorders in the female population.

Disclosures: F.J. Flores-Ramirez: None. **L.M. Riggs:** None. **J.B. Alipio:** None. **M.A. Hernandez:** None. **B. Cruz:** None. **S.H. Braren:** None. **P.A. Serrano:** None. **S.D. Iniguez:** None.

Poster

569. Adolescent Development: Animal Models

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Program#/Poster#: 569.03/A74

Topic: A.09. Adolescent Development

Title: GABAergic disruption in the juvenile prefrontal cortex of Npas4 deficient mice

Authors: *L. COUTELLIER;
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Abstract: Disruption of juvenile GABAergic maturation of the prefrontal cortex (PFC) is associated with cognitive and emotional deficits that characterize psychopathologies including schizophrenia and mood disorders. Understanding these disorders implies the identification of juvenile factors contributing to such GABAergic maturation. Using molecular, pharmacological and behavioral methods in mice, we show that Npas4 could be a significant contributor to the postnatal development of the GABAergic system. We first show sex- and age-dependent Npas4 expression in the PFC of C57Bl/6 mice: males have a higher level of Npas4 mRNA than

females, and in males, Npas4 mRNA level doubles from postnatal day (PND) 21 (childhood) to PND35 (adolescence). We then show that transgenic Npas4 deficient mice display sex-dependent abnormal expression of several pre- and post-synaptic GABAergic markers in the PFC during the juvenile period. These prefrontal GABAergic abnormalities are associated with PFC-dependent cognitive function deficits in males and with depressive-like behavior in females. These behavioral abnormalities are rescued by a chronic treatment with a GABA enhancer during the juvenile period. This treatment also normalizes expression of most of the PFC GABAergic markers. Our data indicate for the first time that Npas4 could contribute significantly to the juvenile maturation of the prefrontal GABAergic system in a sex-dependent way. The study of Npas4 could help us understand susceptibilities to neuropsychiatric disorders that are characterized by prefrontal GABAergic dysfunctions (i.e. schizophrenia; mood disorders). Further analyses in tamoxifen-inducible conditional knockout mice will be conducted to verify the significant contribution of Npas4 during the juvenile period.

Disclosures: L. Coutellier: None.

Poster

569. Adolescent Development: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 569.04/A75

Topic: A.09. Adolescent Development

Title: Environmental enrichment during adolescence alters anxiety, cognitive functioning, and dendritic spine density in male and female rats

Authors: *R. E. BOWMAN[1], J. WAGENBLATT[1], K. BARATELI[2], V. LUINE[2], M. FRANKFURT[3];
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Abstract: Exposure to environmental enrichment (EE) during times of organizational development are known to enhance performance on a variety of cognitive tasks and these behavioral enhancements are associated with morphological changes in the brain. Increasingly, the period of adolescent development is being recognized as a time of sensitivity and continued brain development; however, the effects of EE exposure during adolescence have not been extensively studied. In the current study, male (n=16) and female (n=16) Sprague-Dawley rats were weaned (post-natal day 21) and assigned to a control group or an enriched group. Experimental animals were exposed to 2hr/day of environmental enrichment during post-natal

days 24-42 while the control subjects remained in their home cages, but received equal amounts of daily handling. At 6 weeks of age, all subjects were tested for anxiety (elevated plus maze) and activity (open field), as well as spatial memory (object placement) and non-spatial working memory (object recognition) with inter-trial delays of 1 and 2 hrs. In addition, we measured dendritic spine density in the CA1 region of the hippocampus. Females, regardless of EE treatment, were less anxious than males on the elevated plus maze. However, on the open field, EE had a sexually-differentiated effect in which anxiety was decreased in females, but increased in males, following EE. All groups demonstrated intact spatial memory but performance was enhanced in EE females following a 1 hr inter-trial delay compared to all other groups. Interestingly, while performance was well-above chance for all groups on the object recognition task, both male and female EE groups spent significantly less time with the novel object than their control counterparts following a 2 hr inter-trial delay. Adolescent EE exposure increased dendritic spine density in CA1 basal dendrites in both males and females (20% increase). Together these results indicate that adolescent EE exposure alters both behavior and neuronal morphology, although some effects appear sex-dependent.

Disclosures: R.E. Bowman: None. **J. Wagenblatt:** None. **K. Barateli:** None. **V. Luine:** None. **M. Frankfurt:** None.

Poster

569. Adolescent Development: Animal Models

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Topic: A.09. Adolescent Development

Support: NIH grant U01 AA019972 – NADIA Project.

Title: Voluntary binge-level consumption of ethanol in adolescent rats and the consequences on adult social behavior

Authors: *D. HOSOVÁ, E. I. VARLINSKAYA, L. P. SPEAR;
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Abstract: Initiation of alcohol use occurs predominantly in early adolescence; episodic heavy drinking during this time has long-lasting detrimental consequences. Rat models assessing adolescent heavy drinking often employ intragastric, vapor or intraperitoneal (IP) routes of ethanol administration. Such methods enable precise dosage, but do not account for a realistic drinking pattern; the full dose is given at once, unlike a drinking session, and, in the case of the

IP or vapor route, ethanol does not enter via the gastrointestinal tract. Yet, most models of adolescent voluntary consumption in outbred rat strains rarely produce blood ethanol concentrations (BECs) in the binge range. To determine if there may be an effective method for inducing voluntary binge levels of ethanol consumption in adolescent Sprague-Dawley rats, the present study used a schedule induced polydipsia (SIP) protocol. Adolescent males and females were food deprived to 85% free-feeding body weights from postnatal day (P) 24, and placed into operant chambers for 30 minutes daily from P28-P41. There, pellets were dispensed on a fixed interval 1 minute schedule, with simultaneous free access to either: ethanol in chocolate Boost© (10%, v/v), Boost© alone, or water. Ethanol consumptions in these 30 minute sessions averaged in the binge range (mean BECs > 80 mg/dl) and varied across days, with high consumption days sometimes producing BECs approaching 200mg/dl, followed by several lower consumption days, in repeating cycles. From P77-P87, animals were tested for social interactions and intake of 20% ethanol in a social context, as well as intake when alone, in alternating every other day sessions. These were recorded and scored for time spent drinking and play fighting, an adolescent-typical form of social behavior. As expected, regardless of adolescent exposure condition, adult females consumed nearly twice as much ethanol as males. A significant interaction was found between adolescent exposure and drinking context: whereas adults in the control groups averaged similar intakes in both conditions, adolescent ethanol-exposed animals drank notably more when drinking socially than when alone, in both sexes. Also, intake of animals exposed to ethanol during adolescence (but not control animals) was significantly correlated with level of play fighting, revealing for the first time socially facilitating effects of ethanol in an adult social drinking context - social facilitation that was evident only after adolescent exposure. Current studies are exploring whether this induction of binge levels of ethanol consumption is a function of the schedule per se, and specific to adolescent access.

Disclosures: **D. Hosová:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Developmental Exposure Alcohol Research Center (DEARC), Department of Psychology, Binghamton University, Binghamton, NY 13902-6000. NIH grant U01 AA019972 – NADIA Project. **E.I. Varlinskaya:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Developmental Exposure Alcohol Research Center (DEARC), Department of Psychology, Binghamton University, Binghamton, NY 13902-6000. NIH grant U01 AA019972 – NADIA Project. **L.P. Spear:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Developmental Exposure Alcohol Research Center (DEARC), Department of Psychology, Binghamton University, Binghamton, NY 13902-6000. NIH grant U01 AA019972 – NADIA Project..

Poster

569. Adolescent Development: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 569.06/A77

Topic: A.09. Adolescent Development

Support: CIHR grant

Title: Impact of gonadectomy within the Four Core Genotype mouse model: Evidence that sex steroids shape brain structures via activation as well as organization and that influences of sex chromosomes are independent of hormonal milieu

Authors: *C. CORRE[1], D. A. VOUSDEN[2], S. SPRING[2], E. COX[2], A. METCALF[1], L. R. QIU[1], M. R. PALMERT[1], J. P. LERCH[2];
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Abstract: Understanding the basis of sexual dimorphisms in brain structure and function will likely inform our understanding of sexually dimorphic incidence rates for psychiatric disorders. Using the Four Core Genotype (4CG) mouse model, in which impacts of sex steroids and sex chromosomes are decoupled, we recently showed that steroids and chromosomes influence distinct regions in the mouse brain, and that sex steroids, but not chromosomes, affect learning in the radial arm maze (RAM). Here, we used pre-pubertal gonadectomy within the 4CG model to examine two additional influences on brain development: 1) the dependence of sexual dimorphisms in brain anatomy and behaviour on organizational vs. activational steroid effects; and 2) compensation (the masking of chromosome-dependent sexual dimorphisms by circulating steroids). **Methods** Intact or gonadectomized 4CG mice (XX F, XX M, XY F, XY M; n=9-26/group) were perfused on postnatal day 65 and the brains were scanned using MRI. Automated algorithms were used to compute the volume of 62 brain regions for each mouse, and ANOVAs were performed for each structure and at each voxel to assess effects of sex steroids, sex chromosomes, and gonadectomy. A subset of mice was trained on the RAM for 5 days. **Results** 1. Prepubertal gonadectomy reduced many previously observed sex steroid-dependent effects in brain structure volumes, including the hypothalamus, parieto-temporal lobe, and bed nucleus of the stria terminalis (Fig. 1). 2. Effects of sex chromosome complement in gonadectomized 4CG mice recapitulated those in intact mice: sex steroids did not influence chromosomal effects. 3. In both intact and gonadectomized mice, gonadal sex, but not chromosome complement, affected RAM learning. **Conclusion** While RAM learning depends on organizational effects of sex steroids, both organizational and activational effects influence sex-steroid dependent

dimorphisms in brain structure. No brain area displayed evidence of previously masked effects of sex chromosomes. These findings further our understanding of the shaping of the male and female brain.

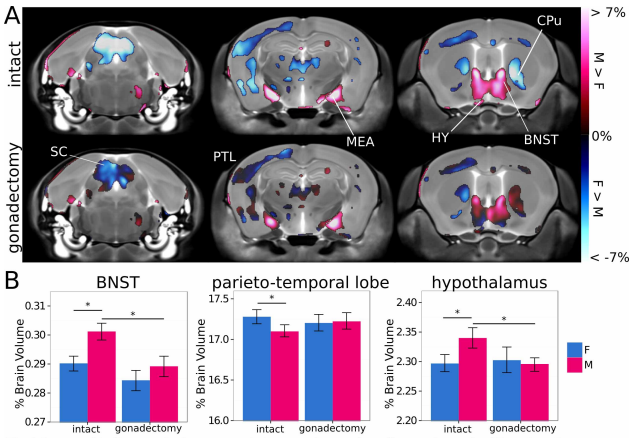

Fig. 1 Sex steroid effects on brain structure in intact and pre-pubertally gonadectomized Four Core Genotype mice. A: Voxel-wise analysis: An ANOVA was performed at each voxel to assess the effects of sex steroids, sex chromosomes, and gonadectomy on local volume. Multiple comparisons were accounted for using the false discovery rate (FDR). Representative coronal slices show areas in which there was a significant (10% FDR) effect of sex steroids on local volume. Slices depict the percent difference in voxel size between intact males and females (top row) or between gonadectomized males and females (bottom row). Gonadectomy reduces sex-steroid dependent effects in many brain structures. B: Volumetric analysis: Gonadectomy reduced or eliminated sex-steroid dependent differences in brain structure volume. SC: superior colliculus, PTL: parieto-temporal lobe; MEA: medial amygdalar nuclei; HY: hypothalamus; BNST: bed nuclei of the stria terminalis; CPu: caudoputamen; F: XX & XY Females; M: XX & XY Males. Error bars are 95% confidence intervals.

Disclosures: **C. Corre:** None. **D.A. Vousden:** None. **S. Spring:** None. **E. Cox:** None. **A. Metcalf:** None. **L.R. Qiu:** None. **M.R. Palmert:** None. **J.P. Lerch:** None.

Poster

569. Adolescent Development: Animal Models

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Topic: A.09. Adolescent Development

Support: NIDA Grant R01DA026854

Title: Unpredictable chronic mild stress during adolescence shifts preference for nicotine and alters gene expression in the ventral tegmental area

Authors: *L. F. ALCANTARA, E. M. PARISE, O. K. SIAL, M. A. GREENWOOD, T. GNECCO, N. J. HARDIMAN, A. I. GONZALEZ, C. A. BOLAÑOS-GUZMÁN; Psychology, Florida State Univ., Tallahassee, FL

Abstract: Many adults report that their first encounter with drugs of abuse was during adolescence, and most common during this time is the initiation of tobacco use. This is troubling

because individuals who begin smoking at a young age have a much harder time trying to quit, suggesting that adolescents are particularly vulnerable to future nicotine dependence. Stress, an essential factor in precipitating mood-related disorders, has been shown to perpetuate nicotine use and change the rewarding properties of nicotine. Surprisingly, the neurobiological basis of this synergistic relationship has been largely understudied in young populations. To further examine the interaction(s) between stress, age and vulnerability to nicotine, adolescent (postnatal day 35) male Sprague Dawley rats were exposed to 4 weeks of unpredictable chronic mild stress (UCMS) and their behavioral reactivity to anxiety-provoking (i.e., elevated plus maze [EPM]), stress-eliciting situations (i.e., forced swim test [FST]), and reward (i.e., sucrose preference) was assessed. Changes in sensitivity to nicotine (0.08, 0.16, 0.24, 0.32 mg/kg) were also assessed using the conditioned place preference (CPP) paradigm. Brain tissue was collected from a separate group of UCMS-exposed rats and changes in gene expression within the ventral tegmental area (VTA) were examined. The VTA was chosen given its crucial role in mediating drug- and mood-related behaviors. Adolescent rats exposed to UCMS spent less time in the open arms of the EPM, displayed decreased latency to immobility and higher total immobility in the FST, and had a reduced preference for sucrose - all behavior outcomes indicative of a depression-like phenotype. Assessment of CPP scores showed that these rats also had a higher preference for the lowest dose (0.08 mg/kg), while showing no preference for the highest dose (0.32mg/kg) of nicotine, which non-stressed, control rats found rewarding. This indicates that stress changes sensitivity to nicotine. Gene expression was measured using rt-qPCR. UCMS-exposed rats showed dysregulation of genes implicated in mood disorders and drug abuse: Delta fos b (Dfosb), the extracellular signal-regulated kinase 1/2 (ERK 1/2), and the early growth response protein 1 (Zif268) were elevated in the VTA when compared to non-stressed controls. This data indicates that chronic stress during adolescence induces an anxiety- and depression-like phenotype while increasing sensitivity to nicotine. This work expands the current knowledge of the interaction between stress and nicotine reward and gives insight into better understanding the genes potentially mediating drug use driven by mood-related disorders.

Disclosures: **L.F. Alcantara:** None. **E.M. Parise:** None. **O.K. Sial:** None. **M.A. Greenwood:** None. **T. Gnecco:** None. **N.J. Hardiman:** None. **A.I. Gonzalez:** None. **C.A. Bolaños-Guzmán:** None.

Poster

569. Adolescent Development: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 569.08/A79

Topic: A.09. Adolescent Development

Title: Repeated ketamine exposure during adolescence produces long-lasting changes in reward sensitivity to drugs of abuse and gene expression in the Nucleus accumbens in adulthood

Authors: *O. K. SIAL[1], E. M. PARISE[1], A. M. GANCARZ[2], L. F. ALCANTARA[1], A. I. GONZALEZ[1], T. GNECCO[1], D. M. DIETZ[2], C. A. BOLAÑOS-GUZMÁN[1];
[1]Florida State Univ., Tallahassee, FL; [2]State Univ. of New York, Buffalo, NY

Abstract: Major Depressive Disorder (MDD) is a highly prevalent and potentially debilitating psychiatric condition affecting approximately 20% of the global population. MDD afflicts up to 10% of adolescents, with nearly 50% of those afflicted considered non-responsive to available treatments. Ketamine (KET), a non-competitive N-methyl-D-aspartate receptor antagonist has shown potential as a rapid-acting and long-lasting treatment for MDD. Unfortunately, these effects are not permanent and it is conceivable that patients will require subsequent exposure to KET. We have recently shown that repeated exposure to KET in adolescent male rats produces behavioral adaptations indicative of a stress-resilient phenotype in adulthood. Given that adolescence is a critical developmental period and that KET has high abuse liability, the lasting neurobiological consequences of repeated KET treatment and its subsequent re-exposure must be characterized. Therefore, this study was designed to assess the effects of re-exposure to KET on behavioral reactivity to rewarding (i.e., drug self-administration, conditioned place preference [CPP]) and aversive stimuli (i.e., forced swim test [FST]) in adult rats pretreated with KET as adolescents. Adolescent male rats were treated with KET (0, 20 mg/kg, twice daily) for 15 consecutive days (postnatal days [PD] 35-49) and then left undisturbed until adulthood. On PD80, rats received a submaximal dose of KET (10 mg/kg) and tested in the FST or for locomotor activity. KET pretreated rats showed increased latency to immobility and decreased total immobility in the FST, and a robust KET-induced locomotor sensitization. Adult rats pretreated with KET as adolescents also showed increased sensitivity to the rewarding effects of KET (5, 10 mg/kg) as measured in the drug self-administration and CPP paradigms as compared to controls. These findings suggest that repeated exposure to KET during adolescence produces increased sensitivity to KET in adulthood. A separate group of adolescent rats were used for assessment of KET-induced biochemical changes in the nucleus accumbens (NAc). Rt-qPCR analysis revealed that pretreatment with KET modulates the expression of genes implicated in depression and drug-addiction. Rats pretreated with KET showed significant decreases in TrkB, BDNF, Akt, dFosB and ERK2 mRNA when compared to controls. Conversely, there was an increase in CREB, GSK3B, GluR2, and GluR3 mRNA expression. Together these findings indicate that repeated KET during adolescence increases sensitivity to subsequent KET in adulthood, and implicate the intracellular pathways mediating responsivity to stress and KET re-exposure.

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Poster

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Program#/Poster#: 569.09/A80

Topic: A.09. Adolescent Development

Support: NIMH Grant MH103939

Title: Repeated Ketamine treatment produces a stress-resistant phenotype in adolescent mice

Authors: ***E. M. PARISE**, L. F. ALCANTARA, O. K. SIAL, A. I. GONZALEZ, N. J. HARDIMAN, C. A. BOLAÑOS-GUZMÁN;
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Abstract: Major Depressive Disorder (MDD) is a leading cause of disability and among the top leading causes of disease burden in the world. MDD, also common in pediatric populations, affects about 10% of children and adolescents at any given time. Early life MDD can be highly debilitating, with lasting negative consequences extending into adulthood. Although available treatments are generally effective and safe, they are suboptimal. Recently, Ketamine (KET), a non-competitive N-methyl-D-aspartate receptor antagonist, has shown promise as a rapid acting and potentially long-lasting antidepressant in patients with MDD. Unfortunately, initial clinical assessments indicate that acute ketamine is not sufficient to produce lasting effects, and that repeated KET treatment may be more effective. Nevertheless, very little is known about the effects of KET treatment on subsequent stress responding, especially during adolescence. Therefore, this study was designed to assess the effects of KET treatment on behavioral reactivity to stress in adolescent (postnatal day [PD] 35) mice. An initial experiment was conducted to determine KET antidepressant activity in naïve male adolescent C57BL/6J. PD35 mice received an acute injection of KET (0, 5, 10, 20 mg/kg) and 24 h later their behavioral reactivity to anxiety- and stress-eliciting situations (i.e. social interaction test [SIT], and forced swim test [FST]) was assessed. KET significantly increased time spent with a social target in the SIT and decreased total immobility in the FST, responses indicative of an antidepressant-like response. Next, we assessed the ability of an acute dose of KET to reverse the effects of chronic social defeat stress (CSDS) during adolescence. PD35 mice were subjected to 10 days of CSDS, treated with a single dose of KET (0, 10, 20 mg/kg) 1 h after the last defeat and then tested in the

SIT and FST 24 h later. Although both doses of KET significantly reduced total immobility in the FST, only the 10mg/kg dose increased time spent in the interaction zone. Finally, we determined whether repeated KET during adolescence could block the effects of CSDS. Separate groups of adolescent male mice were treated once daily with KET (0 or 10 mg/kg) for 15 consecutive days (PD 35-49). After a 7 d washout period, mice were subjected to 10 d of CSDS and 24 h after the last stress session, exposed to the SIT and FST. KET significantly blocked the CSDS-induced deficits in the SIT and FST. Together, these findings indicate that KET produces a stress-resistant phenotype in adolescent male mice and support the notion that repeated KET treatment may provide superior efficacy as an antidepressant.

Disclosures: E.M. Parise: None. **L.F. Alcantara:** None. **O.K. Sial:** None. **A.I. Gonzalez:** None. **N.J. Hardiman:** None. **C.A. Bolaños-Guzmán:** None.

Poster

569. Adolescent Development: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 569.10/A81

Topic: A.09. Adolescent Development

Title: Oxycodone exposure during adolescence and adulthood dysregulates striatal gene expression and facilitates hydrocodone-seeking in rats

Authors: *M. A. GREENWOOD[1], L. F. ALCANTARA[1], E. M. PARISE[1], C. PIEKARSKI[2], O. K. SIAL[1], J. BEVERLEY[2], H. STEINER[2], C. A. BOLAÑOS-GUZMÁN[1];
[1]Neuroscience, Psychology, Florida State Univ., Tallahassee, FL; [2]Dept. of Cell. and Mol. Pharmacol., Rosalind Franklin Univ. of Med. and Sci., Chicago, IL

Abstract: Opiate drugs are prescribed for short-term treatment of mild to moderate pain. Due to the ease of access and availability of these medications, illicit use of prescription opiates has become a growing health concern in the United States. Nonmedical use of prescription opiates can facilitate transition to long-term opiate abuse and dependence. In spite of the high rates of medication abuse by adults and adolescents, the neurobiological changes that occur with chronic opiate exposure are poorly understood. Therefore, the purpose of this study was to characterize the biological consequences of chronic oxycodone exposure in adolescent and adult rats, namely in the striatum, a brain region implicated in habit formation and compulsive behaviors related to drug addiction. Adolescent (postnatal day [PD] 35) and adult (PD 65) male Sprague-Dawley rats were treated with once-daily subcutaneous injections of oxycodone on a schedule of escalating doses (10-70 mg/kg), over 7 consecutive days. Two hours after their final injection, rats were

sacrificed and tissue collected. Gene expression was measured by *in situ* hybridization in a total of 23 striatal sectors that represented all major functional domains of the striatum. Opioid peptide markers selectively expressed by direct (dynorphin, DYN) and indirect (enkephalin, ENK) striatal output pathways were assessed. Results indicate that chronic oxycodone treatment reduces ENK expression throughout the striatum regardless of age of exposure. No differences in expression of DYN (or substance P) as a function of age or pre-treatment were detected. Adolescents also displayed reduced expression of the immediate early gene Zif268 throughout the rostral striatum, while both adolescents and adults showed increased Zif268 expression in the lateral part of the caudal striatum. Given that ENK and Zif268 have been implicated in addiction-related behaviors, additional cohorts of rats were chronically treated with oxycodone and subsequently underwent place conditioning to 1 mg/kg hydrocodone. Post-conditioning, time to extinguish their place preference was measured. Adolescents developed a preference regardless of pretreatment, whereas only adults pretreated with oxycodone developed a preference for environments paired with hydrocodone. However, only adolescents pretreated with oxycodone required significantly more time to extinguish their established place preference. These findings suggest that chronic oxycodone exposure modulates drug-seeking behaviors in adolescent and adult rats possibly via differential gene regulation in striatal output pathways, including reduced ENK function in the indirect pathway.

Disclosures: **M.A. Greenwood:** None. **L.F. Alcantara:** None. **E.M. Parise:** None. **C. Piekarski:** None. **O.K. Sial:** None. **J. Beverley:** None. **H. Steiner:** None. **C.A. Bolaños-Guzmán:** None.

Poster

569. Adolescent Development: Animal Models

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Program#/Poster#: 569.11/A82

Topic: A.09. Adolescent Development

Support: NIH Grant

Title: Pubertal timing depends on TRPC2 signaling in mice

Authors: ***D. R. PFAU**[1], S. M. BREEDLOVE[2], C. L. JORDAN[3];
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Abstract: Function of the vomeronasal organ is critically tied to the transient receptor potential cation channel, subfamily C, member 2 (TRPC2). There is evidence that a subpopulation of TRPC-expressing neurons in the vomeronasal organ (VMO) exert control over the timing of puberty in female mice (Oboti et al. 2014, BMC Biology 12: 31) but whether TRPC2 neurons in the VMO have the same role in male mice is not known. To address this question, we monitored pubertal timing in male and female mice that had the TRPC2 gene knocked out (KO; Jackson Laboratories Strain Name: B6;129S1-Trpc2tm1Dlc/J; Stock Number: 021208). TRPC2 KO mice were on a mixed 129S1 and C57BL/6 genetic background and compared to wildtype (WT) controls of the same mixed background. Pubertal onset was based on preputial separation in males and vaginal opening in females. Body weight was also measured at weaning. We found a significant delay in pubertal onset for both male ($F(1,31)=10.72$, $p=0.003$, $d=1.3$) and female ($F(1,44)=13.18$, $p=0.001$, $d=1.0$) KO mice. Puberty was delayed by about 2 days for KO males (KO = 29.560 ± 0.57 (Mean + SEM) vs. WT = 27.12 ± 0.57) and by about a day for KO females (KO = 29.545 ± 0.61 vs. WT = 28.059 ± 0.40). This is the first demonstration that TRPC2 plays a role in pubertal timing in male mice and confirms the previous finding of an effect of TRPC2 on pubertal timing in female mice. While body weights are reportedly higher in KO mice at birth and at six days postnatal, we find that body weight was significantly reduced at weaning for KO mice: KO females weighed almost 3 grams less than WT females ((13.268g ± 0.678) vs. 16.044g ± 0.655, respectively; $F(1,28)=6.38$, $p=0.018$, $d=0.86$)) at weaning (22 days postnatal) whereas KO males weighed around 1.5 grams less than WT males (14.005 ± 0.568 vs. 15.718 ± 0.765, respectively; $F(1,30)=4.846$, $p=0.036$, $d=0.78$) at weaning. This effect on body weight at weaning may reflect poor quality lactation seen in KO dams (Hasen and Gammie 2011, Behav Brain Res 217: 347). Future studies will examine the potential influence of TRPC2 signaling on the adult neural systems mediating aggression and sex-specific behaviors that depend on the detection and discrimination of sex-specific chemical cues.

Disclosures: **D.R. Pfau:** None. **S.M. Breedlove:** None. **C.L. Jordan:** None.

Poster

569. Adolescent Development: Animal Models

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Program#/Poster#: 569.12/A83

Topic: A.09. Adolescent Development

Support: NIH grant MH099625

Title: Development of dopaminergic fibers in the medial prefrontal cortex of male and female rats during adolescence

Authors: J. WILLING[1], J. M. BRODSKY[1], L. R. CORTES[1], T. KIM[1], *J. M. JURASKA[2]; [1]Psychology and Program in Neurosci., [2]Psychology, Univ. of Illinois, Champaign, IL

Abstract: Adolescence is a critical developmental period associated with neuroanatomical changes that are accompanied by improved cognitive performance. The medial prefrontal cortex (mPFC), a region that mediates executive function, undergoes extensive reorganization during the adolescent period. Data from our lab show that neuron number and the dendritic tree in the mPFC change from preadolescence to adulthood in a sex-specific manner. Less is known regarding the development of dopaminergic fibers innervating this region. Specifically, while it has been demonstrated that the density of dopaminergic fibers increases between adolescence to adulthood in male rats, the precise trajectory of these changes across adolescence, in both males and females, remains unexplored. In the present study, we track changes in the volume of tyrosine hydroxylase (TH) immunoreactive axons in distinct layers of the male and female mPFC at multiple time points from preadolescence to adulthood (P25, P35, P45, P60 and P90). The density of fibers was multiplied by the volume of the region for each animal to give the total amount (volume) of TH fibers. Both males and females gained TH fiber volume in layers 1 and 2/3, with significant increases early between P25 and P35. In layer 5, there was a gradual increase in TH fiber volume in both males and females, with a significant difference between P25 and P90 rats. Analysis of "skeletonized" images, measures fiber length (not width), yielded the same trends, suggesting that increases in TH fiber volume were the result of increased total length of fibers. In summary, dopaminergic innervation of the mPFC increases during adolescence with similar trajectories in male and female rats. Elucidation of the precise timing of dopaminergic innervation of the mPFC, along with other developmental changes, may help provide insight into mental illnesses characterized by mPFC dysfunction such as schizophrenia, depression and addiction that frequently manifest during adolescence.

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Poster

569. Adolescent Development: Animal Models

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Program#/Poster#: 569.13/A84

Topic: A.09. Adolescent Development

Title: Environmental enrichment promotes adaptation to environment rearrangement in younger but not older adolescent rats

Authors: *D. E. COBB, K. L. PATTERSON, R. GUCWA, A. J. ROSSI, E. A. ARTZ, A. P. BRUNSON, M. C. ZRULL;
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Abstract: Experiences, such as environmental enrichment (EE), that allow for investigation and informal learning can lead to brain changes and alter novelty seeking and exploratory behaviors, and adolescence is a developmental period during which these behaviors are apt to change. We investigated the effect of EE during adolescence on preference for location of known objects (constant or rearranged) using an object-in-place (OiP) task. In addition, neural activation in the dentate gyrus (DG) and CA1 region of hippocampus, which is implicated in the detection of novel spatial relationships, was investigated using the neural activity marker c-fos. Adolescent Long-Evans rats (n=16) were exposed to EE between postnatal days (pnd) 25 and 48. Age-matched controls (n=16) experienced a non-enriched home-cage. Two-trial OiP testing occurred on pnd 36 and 50 with two delays (15 and 60 min) in an open field containing four objects. Exploration time and time in direct contact with the rearranged objects was measured at each delay. After testing, brain tissue was processed to examine levels of neural activity in DG and CA1 using immunohistochemistry for c-fos. At pnd 36, EE animals spent more time with all objects (M=45-s, SD=12.3) than no-EE animals (M=32-s, SD=13.1) across both delays ($p<.01$). EE rats spent about half their time exploring rearranged objects at both delays, which contrasted with no-EE controls spending more time (+23%) and less time (-32%) with the switched objects at the 15 and 30 min delays ($p<.05$). At pnd 50, EE rats spent less time on average with the objects (M=29-s, SD=15.1) than no-EE animals (M=41-s, SD=21.1) across both delays ($p<.05$). However, both EE and control rats spent similar proportions of time with rearranged objects at the 15 min (M=0.66, SD= 0.22) and 60 min (M=0.38, SD= 0.23) delays. Analysis of c-fos tissue showed 24.4% fewer active neurons in CA1 of EE rats than no-EE rats ($p<.05$) and no difference between groups in DG neural activation suggesting some impact of EE on hippocampal processing evoked by the OiP task. While neural data support the conclusion that EE animals recognize novelty, behavioral results indicate a decrease in novelty preference in younger, but not older adolescent animals, because of EE. EE promotes adaptation to novelty in younger but not older adolescent rats. These results indicate that adolescence may, in fact, be a critical period for the impact of EE and that EE that takes place earlier in adolescence is most effective at reducing risk-taking behaviors, such as novelty seeking or preference.

Disclosures: D.E. Cobb: None. **K.L. Patterson:** None. **R. Gucwa:** None. **A.J. Rossi:** None. **E.A. Artz:** None. **A.P. Brunson:** None. **M.C. Zrull:** None.

Poster

569. Adolescent Development: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 569.14/A85

Topic: A.09. Adolescent Development

Support: NIGMS SC2GM109811

Title: Ketamine exposure during adolescence increases sensitivity to reward-related stimuli in adulthood

Authors: *L. M. RIGGS[1], J. B. ALIPIO[2], M. A. HERNANDEZ[2], K. L. SHAWHAN[2], B. CRUZ[1], D. SANCHEZ[2], A. R. ZAVALA[3], S. D. IÑIGUEZ[1];
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Abstract: Pediatric depression was not well recognized until relatively recent. Today, however, major depressive disorder (MDD) is commonly diagnosed in children and adolescents, and when left untreated, may result in negative consequences that extend into adulthood. It is estimated that children and adolescents who suffer from MDD are likely to develop conduct and anxiety disorders, and that up to 25% eventually develop substance abuse disorder. Consequently, this has resulted in a disproportionate increase in the prevalence of antidepressants prescribed to populations below 20 years of age. Recently, the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine, has been shown to alleviate symptoms of MDD in individuals that suffer from treatment-resistant depression. However, little is known about the potential long-term consequences of exposure to ketamine during early development. This is particularly important to examine, given ketamine's abuse potential. To address this issue at the preclinical level, we examined whether ketamine exposure during adolescence results in long-lasting changes in sensitivity to the rewarding effects of sucrose (i.e., natural reward), as well as cocaine (i.e., drug reward). Specifically, male c57BL/6 mice were exposed to ketamine (0 or 20 mg/kg) during adolescence (postnatal days [PD] 35-49) and were later assessed in adulthood (PD 70+) on behavioral responsivity to a sucrose solution (1%), or cocaine (0, 5, 10, or 20 mg/kg) place conditioning (CPP). Here we show that adult mice pre-treated with ketamine during adolescence displayed enhanced preference for a sucrose solution, as well as environments previously paired with moderately low doses of cocaine, when compared to saline pre-treated controls. Together, our findings suggest that exposure to ketamine during adolescence increases sensitivity to both natural and drug-rewards, later in life.

Disclosures: **L.M. Riggs:** None. **J.B. Alipio:** None. **M.A. Hernandez:** None. **K.L. Shawhan:** None. **B. Cruz:** None. **D. Sanchez:** None. **A.R. Zavala:** None. **S.D. Iñiguez:** None.

Poster

569. Adolescent Development: Animal Models

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Topic: A.09. Adolescent Development

Support: Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPq/Brazil - grant 476634/2013-0

Title: Effects of single bout of treadmill exercise on epigenetic parameters in hippocampus from adolescent female and male Wistar rats

Authors: *I. R. SIQUEIRA, L. C. F. MEIRELES, K. BERTOLDI, C. G. BASSO, L. R. CECHINEL, V. R. ELSNER;
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Abstract: DNA methylation at promoters and histone acetylation have been linked to sex-specific responses, as well some proteins related to DNA methylation are related to sexual dimorphic in the rodent amygdala during the critical period for sexual differentiation. However there are no studies, to our knowledge, reporting DNA methylation and histone acetylation machineries in hippocampus of female and male adolescent rodents. Moreover it has been demonstrated that different exercise protocols are able to alter epigenetic marks, such as DNA methyltransferases (DNMTs) content and histone deacetylases (HDACs) activity in hippocampus of young adult and aged male Wistar rats. Interestingly, a decreased striatal HDAC activity was found at 1 h and 18 h after a single session of exercise in adolescent male Wistar rats. Our aim was to investigate HDAC activity and DNMT1 content in hippocampi of adolescent female and male Wistar rats submitted to a single session of treadmill exercise at different time-points after the exercise, 1 hour and 18 hours. The Local Committee (CEUA/UFRGS) approved all handling and experimental conditions (nr.21449). Male and female Wistar rats were maintained under standard conditions. The rats were submitted to a single session of treadmill (20 min). The samples were obtained from 39-day-old rats at different time-points after the exercise, 1 hour and 18 hours. Three-way ANOVA showed a significant effect of gender and time point after the single exercise session, since female had higher HDAC global activity than male Wistar rats. Moreover, a temporal pattern in HDAC activity was observed, given that this parameter was enhanced in the early morning (18 hours group) than the afternoon (1 hour group). Besides, there was a trend of interaction between gender and time point factors ($p=0.08$). Additionally, three-way ANOVA evidenced that hippocampi of female Wistar rats exhibited higher levels of DNMT1 than male. Our data can suggest that DNA

methylation and histone acetylation machineries, specifically the enzymes HDAC and DNMT1, can be related to sex-specific responses.

Disclosures: I.R. Siqueira: None. **L.C.F. Meireles:** None. **K. Bertoldi:** None. **C.G. Basso:** None. **L.R. Cechinel:** None. **V.R. Elsner:** None.

Poster

569. Adolescent Development: Animal Models

Location: Hall A

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Program#/Poster#: 569.16/A87

Topic: A.09. Adolescent Development

Title: Environmental enrichment reverses down-regulation of hippocampal brain-derived neurotrophic factor (BDNF) in male rats following early-life inflammatory challenge

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Abstract: In the laboratory, environmental enrichment (EE) is generally designed using a multifactorial approach incorporating novelty (i.e. alternating toys and their locations within an animal's cage) alongside opportunities for physical activity (i.e. increased cage space) and social engagement facilitated through group housing. This type of rearing is often utilized to evaluate its neuroprotective and rehabilitative potential as a translational intervention for complications associated with stroke, Huntington's disease, traumatic brain injury, and even psychological stressors. Typically the utility of EE is evaluated in response to challenges that occur in adulthood but another stream has focused this environmental intervention on pediatric and long-term consequences following early-life adversity. Stemming from evidence that EE can rescue the brain from early-life trauma we are interested in how the various components of enrichment (i.e. novelty, physical space, social engagement) may contribute to the reversal of the behavioral and neural disruptions that accompany maternal immune activation (MIA). In the present study, standard housed female Sprague-Dawley rats were administered either the inflammatory endotoxin lipopolysaccharide (LPS; 100ug/kg) or pyrogen-free saline (equivolume) on gestational day 15. Following weaning on postnatal day (P)22, male and female offspring remained in same-sex pair-housed standard cages until P50 at which point they were randomized into one of three conditions: EE (groups of 4-6 animals housed in a large multi-level cage with toys, tubes and ramps), Colony Nesting (CN; groups of 4 animals socially-housed in a larger style cage), or Standard Care (SC; animals pair-housed in standard cages). Six weeks later we collected hippocampus and prefrontal cortex (n = 7-9) and evaluated these structures for brain-

derived neurotrophic factor (BDNF) and TrkB receptor gene expression (normalized to GAPDH) using qPCR methods. Overall, MIA resulted in a sex-specific down-regulation of BDNF gene expression in the hippocampus of male rats, which was only rescued by EE housing. Our next step is to evaluate the accompanying social behavior data and follow up with further qPCR and protein quantification. Given concerns that behavioral and neural changes in offspring may be associated with inflammation (i.e. sickness) during pregnancy, this ongoing research offers some assurance that interactions between components of the environment (i.e. novelty, physical space, and social engagement) could offer rehabilitative options following early-life exposure to inflammation and other developmental adversities.

Disclosures: **A. Khoury:** None. **M. MacRae:** None. **A.C. Kentner:** None.

Poster

569. Adolescent Development: Animal Models

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Topic: A.09. Adolescent Development

Support: NIH NRSA Grant F31NS092371

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Title: The effects of voluntary exercise on oligodendrocyte development and myelin in juvenile mice and in cuprizone treated adult mice

Authors: *L. G. TOMLINSON, P. HUANG, H. COLOGNATO;
Stony Brook Univ., Stony Brook, NY

Abstract: Voluntary Exercise is known to promote adult hippocampal neurogenesis in rodents, while the extent to which exercise influences oligodendrocyte lineage development and myelination remains unclear. However, some studies have found that voluntary wheel running promotes oligodendrocyte precursor (OPC) differentiation in adult rodents, and a recent study has found that neuronal activity in the premotor cortex promotes oligodendrocyte differentiation and myelination. However, it remains unknown whether exercise can influence myelination during late juvenile development, and if so, whether a critical period for this effect exists, as has been shown for the negative effect of social isolation on myelination. In addition, while voluntary exercise has also been shown to delay symptom onset and reducing damage severity in

some demyelinating mouse models, the degree to which voluntary exercise influences OPC development and myelination dynamics remains unknown. To investigate the effects of voluntary exercise on oligodendrocyte development in juvenile mice, we used two approaches. First, mice at 4, 5, or 8 weeks of age were given free access to running wheels or not for 4 weeks, followed by an assessment of proliferating (Ki67+) OPCs and newly-born EdU+ OPCs (NG2+) and oligodendrocytes (CC1+) in several brain regions including the corpus callosum, prefrontal and motor cortices. Second, using a similar experimental design, we conditionally labeled OPCs with YFP in PDGFaR-CreERT:RosaYFP transgenic mice and analyzed the densities of newly-born YFP+ OPCs and oligodendrocytes. We observed both increased OPC proliferation and increased oligodendrocyte development, and noted an age-dependent decrease in some of the effects such that the more robust exercise-induced changes occurred selectively in younger mice, indicative of a critical window for optimal exercise-regulation of OPC development. To gain insight into exercise-regulated oligodendrocyte lineage dynamics during de- and remyelination, we fed both exercising and non-exercising adult mice cuprizone for 4.5 weeks, then assessed myelin (MBP) levels in the motor cortex. Our preliminary findings indicate an increase in MBP levels in the motor cortex of exercising cuprizone-treated mice relative to that in sedentary cuprizone-treated mice. Overall the results suggest that voluntary exercise influences oligodendrocyte development in juvenile mice, an effect that is attenuated as mice reach adulthood. However in adult mice following myelin damage, myelin is once again modulated by exercise, suggesting that exercise-regulated myelin plasticity can be reactivated following injury.

Disclosures: L.G. Tomlinson: None. **P. Huang:** None. **H. Colognato:** None.

Poster

569. Adolescent Development: Animal Models

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Topic: A.09. Adolescent Development

Support: Young Researchers in Psychology 2014 - University of Costa Rica

Support Found for Final Graduation Work - University of Costa Rica

Title: Grooming as a de-arousal behavior underlying novelty habituation: An effect potentiated by environmental enrichment

Authors: *M. ROJAS[1,2], J. C. BRENES[2], J. FORNAGUERA[2], A. MORA-GALLEGOS[2];
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Abstract: The open field test (OFT) has been extensively used for assessing exploratory behavior, memory, and anxiety-related traits in rodents. Previous evidence suggests that early environmental enrichment (EE) reduces psychomotor reactivity to novelty in the OFT, as compared with animals reared in standard housing (SH). A detailed analysis of OFT activity has shown that EE rats progressively increased self-grooming as locomotion reduced. A preliminary observation revealed that, among the different types of grooming, EE particularly increases the so-called sequential or type 3 grooming (i.e., snout-head-torso liking). Since grooming behavior has also been associated with pain, stress, and thermoregulation, the question of whether increases in grooming behavior can be taken as an indicator of novelty habituation potentiated by EE has not been fully elucidated. In the first experiment, we evaluate the effects of housing conditions on novelty habituation within a 10-min OFT and between two independent OFT conducted 30 days apart. After a baseline OFT, rats were housed either in SH or EE from post natal day (PND) 35, and were evaluated at PND65 and 95 in such a test. In a second experiment, we aimed to test whether grooming behavior, specifically the type 3, is related to novelty habituation independently from EE. Therefore, non-enriched rats were exposed to a 15-min OFT during four consecutive days, expecting that repeated exposition to the same environment increases familiarity and, in consequence, grooming behavior. In a final experiment, SH rats were i.p. treated with the glutamate receptor antagonist (MK-801) to test whether blocking the acquisition of OFT memory prevents grooming behavior to appear in further expositions to the same environment. Evidence will be provided about the putative role of grooming behavior in a non-associative learning process -namely novelty habituation in the OFT- following the assumption that grooming may be a de-arousal behavior belonging to the risk-assessment repertoire of the rat, which is affected by environmental enrichment.

Disclosures: **M. Rojas:** None. **J.C. Brenes:** None. **J. Fornaguera:** None. **A. Mora-Gallegos:** None.

Poster

569. Adolescent Development: Animal Models

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Support: CONACyT Grant 662350

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Title: Juvenile amphetamine exposure does not induces long-term alterations in exploratory behavior and neural morphology of limbic regions in the rat

Authors: *H. TENDILLA, SR, L. ARROYO-GARCÍA, I. CAMACHO-ÁBREGO, G. FLORES;
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Abstract: Amphetamine (AMPH) is a psychostimulant widely used for therapeutic as well as recreational purposes. This substance is a treatment of choice for children with attention deficit hyperactivity disorder (ADHD) despite the lack of preclinical and clinical information about its long-term effects. The controversy surrounding the use of AMPH in children is, because it has been demonstrated that the psychostimulant exposure during the neurodevelopment significantly affects this process, which is essential to generate adequate neural networks for the optimum brain function in the individual. In addition, previous results of our group showed that AMPH exposure in pregnant rats induces physiological and behavioral changes in the offspring at prepuberal and postpuberal ages. On the other hand, several reports have proved that AMPH is capable to modify the morphology of neurons in some regions of the limbic system related to some psychiatric conditions such as substance abuse behavior, major depression and schizophreniform disorder. In this protocol we studied the influence of low dose AMPH exposure (similar to those used in children with ADHD) during juvenile age in healthy rats on exploratory behavior and neural morphology of limbic system areas at three ages: prepuberal, puberal and postpuberal. The behavioral test to evaluate the exploratory behavior was the locomotor activity protocol, in which AMPH alters locomotor activity in prepuberal rats, without changes at puberal and postpuberal age compared with controls. Besides Golgi-Cox staining method was used to describe the neural morphology of four limbic regions: prefrontal cortex, nucleus accumbens, hippocampus and amygdala, showing that AMPH induces changes at prepuberal and puberal ages on the arborization and spine density of these neurons, but interestingly these changes does not persist at postpuberal age. Our findings suggest that even the early-life AMPH exposure does not induces long-term behavioral and morphological changes, it causes alterations at puberal age in the limbic system networks, a stage of life strongly associated to the development of substance abuse behaviors.

Disclosures: H. Tendilla: None. **L. Arroyo-García:** None. **I. Camacho-Ábrego:** None. **G. Flores:** None.

Poster

569. Adolescent Development: Animal Models

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Program#/Poster#: 569.20/A91

Topic: A.09. Adolescent Development

Support: UCLA Division of Life Sciences Recruitment and Retention Fund (Izquierdo)

Title: Learning, socioemotional behavior, and striatal dopamine D1 receptor expression after adolescent drug exposure

Authors: *A. IZQUIERDO, H. POZOS, A. DE LA TORRE, A. STOLYAROVA, S. DESHIELDS, J. CEVALLOS, J. RODRIGUEZ;
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Abstract: Adolescents, when diagnosed with ADHD or Major Depression, are frequently prescribed psychotropic medications. The introduction of methylphenidate (MPH) and fluoxetine (FLX) may impact brain development, potentially leading to long-lasting changes in behavior and cognition. These drugs have been studied for their effects on addiction vulnerability and emotion but not extensively for their enduring effects on cognitive flexibility. In Experiment 1, male and female adolescent Long Evans rats were treated with MPH or FLX for 15 days and compared to treatment with methamphetamine (mAMPH) and saline (SAL). On day 0, 7 and 15 of treatment, novel conspecifics were assessed for duration of social play and nonsocial behavior. Following drug washout, and now in adulthood, rats were tested on pairwise discrimination and reversal learning, a test of cognitive flexibility. We found sex differences in rates of initial discrimination learning, with males showing faster acquisition than females, but no sex by treatment interaction. MPH treatment impaired the accuracy of reversal learning performance (main effect of treatment and treatment group x session interaction). Analysis of reversal learning microstructure revealed the MPH group was faster to touch the stimulus and collect the reward on correct trials compared to SAL. There was also a significant sex by MPH treatment effect in the duration of both social and nonsocial behaviors on Day 7 and 15. In Experiment 2 we assessed activity on the elevated plus maze and sucrose preference in adulthood after adolescent MPH. There were sex, but not treatment group, differences in anxiety wherein females displayed anxiogenic responses. This anxiogenic response may explain the sex differences in learning in Experiment 1. We found no treatment or sex differences in sucrose preference. We then assessed expression of striatal dopamine D1 and D2 receptors via ELISA in tissue collected from animals in each experiment. We found significant elevations in striatal D1 expression in the MPH and mAMPH-treated animals and D2 in MPH-treated females in tissue collected after learning. No differences were found in expression levels from tissue collected within a week of treatment. Collectively these findings suggest that learning and MPH/mAMPH interact to prolong a window of enhanced striatal D1 expression, when otherwise these receptors

would be pruned. Ongoing analyses include measures of synaptic remodeling in both frontal cortex and amygdala in these animals.

Disclosures: **A. Izquierdo:** None. **H. Pozos:** None. **A. De La Torre:** None. **A. Stolyarova:** None. **S. DeShields:** None. **J. Cevallos:** None. **J. Rodriguez:** None.

Poster

569. Adolescent Development: Animal Models

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Topic: A.09. Adolescent Development

Support: DPU-RFUMS Pilot Grant

Title: Repeated social defeat stress during adolescence impairs the maturation of GABAergic function in the adult prefrontal cortex

Authors: *E. FLORES-BARRERA[1], D. R. THOMASES[1], A. CABALLERO[1], J. S. CARTER[2], K. E. GRANT[2], J. A. ROSENKRANZ[1], K. Y. TSENG[1];
[1]Cell. and Mol. Pharmacol., Rosalind Franklin Univ., North Chicago, IL; [2]Dept. of Psychology, DePaul Univ., Chicago, IL

Abstract: Early life exposure to emotionally salient stressors is thought to contribute to the development of maladaptive behavioral patterns later in life, many of which are associated with aberrant functioning of prefrontal-mediated cognitive processing. However, the mechanisms underlying such developmental disruption remain unclear. Here we asked whether a disruption of prefrontal maturation could underlie the enduring cognitive impairments resulting from repeated social stress during adolescence (from postnatal day -P- 32 to P38). Using electrophysiological measures, we found that the normal inhibitory control of afferent drive is lacking in the adult prefrontal cortex (PFC) of rats that underwent adolescent social defeat. Results from local field potential recordings and ventral hippocampal stimulation revealed that the pattern of prefrontal response observed in the social defeat stress group resembles that seen in the immature PFC of naïve juvenile rats. At the cellular level, such inhibitory disruption in the PFC was associated with a state of increased AMPA/GABA ratio in layer V pyramidal neurons, mainly due to a selective downregulation of local GABAergic transmission. A similar dysregulation of prefrontal GABAergic function was observed in rats that underwent social defeat stress during the P42-48 adolescent period. However, no deficits in PFC inhibition were observed when the repeated social defeat stress was presented during late adolescence (i.e., P50-

55) or adulthood (P75-80). Collectively, these results indicate that social defeat stress during early and mid-adolescence had the most potent and enduring impact on PFC function and maturation, in particular at the level of local GABAergic function. As fine-tuning of PFC output and behavior are highly dependent on the activity of local inhibitory interneurons, impaired GABAergic maturation resulting from social defeat stress during adolescence is expected to elicit enduring deficits in prefrontal-dependent cognitive functions.

Disclosures: E. Flores-Barrera: None. **D.R. Thomases:** None. **A. Caballero:** None. **J.S. Carter:** None. **K.E. Grant:** None. **J.A. Rosenkranz:** None. **K.Y. Tseng:** None.

Poster

569. Adolescent Development: Animal Models

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Program#/Poster#: 569.22/A93

Topic: A.09. Adolescent Development

Support: NIGMS SC2GM109811

Title: Enduring effects of fluoxetine on spatial memory performance in adolescent and adult male c57bl/6 mice

Authors: *J. B. ALIPIO[1], L. M. RIGGS[2], L. F. ALCANTARA[3], S. D. INIGUEZ[1]; [1]Psychology, Univ. of Texas at El Paso, El Paso, TX; [2]Psychology, California State Univ., San Bernardino, CA; [3]Psychology, Florida State Univ., Tallahassee, FL

Abstract: Epidemiological reports indicate that mood-related disorders are common in children and adolescents. The prevalence of adolescent clinical depression has resulted in parallel increases in the prescription of Fluoxetine (FLX) and related serotonin reuptake inhibitor antidepressants within this population. Although such treatments can last for years, very little is known about the long-term consequences of antidepressant exposure during developmental periods prior to adulthood on memory performance later in life. Thus, we exposed adolescent (postnatal day [PD] 35) and adult (PD65) male c57BL/6 mice to FLX (0 or 20 mg/kg) for 15 consecutive days. We then assessed animals' behavioral performance on the Morris Water Maze spatial memory task three-weeks after antidepressant exposure. Specifically, mice were trained to find the location of a submerged escape platform on a single day task (8 training trials), and memory for the platform location was re-tested after a 24 hr delay (distance traveled and velocity). To increase the demands of the spatial task, the mice returned to the spatial task once again 24 hr later, and completed a probe trial (escape platform absent), and time to reach the

quadrant of the target platform location, as well as total time spent in the quadrant were recorded. We found that FLX exposure, regardless of age, did not influence spatial memory acquisition on the training day. In addition, no differences between the groups were observed when spatial memory was examined 24 hr after training. Conversely, mice exposed to FLX during adolescence, but not adulthood, swam longer distances to reach the location of the missing platform, when tested 48 hr after training (probe trial). Together, our results suggest that as the demands of the spatial memory task increase, spatial memory deficiencies become apparent in adult mice exposed to FLX during adolescence.

Disclosures: J.B. Alipio: None. **L.M. Riggs:** None. **L.F. Alcantara:** None. **S.D. Iniguez:** None.

Poster

569. Adolescent Development: Animal Models

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Program#/Poster#: 569.23/A94

Topic: A.09. Adolescent Development

Title: Enrichment of young adolescent rats promotes balanced exploration of a simple environment

Authors: *E. A. ARTZ, H. L. JOHNSON, S. J. SNOUSE, T. J. ARNOLD, Z. H. RICHARDSON-BULL, S. A. BLAKE, M. C. ZRULL;
Appalachian State Univ., Boone, NC

Abstract: For many mammals, adolescence is a time of development that features changes in sensation-seeking, response to novelty, and preference. Environmental enrichment (EE), such as an opportunity to interact with novel objects and conspecifics in a known or unknown environment, can influence exploration and novelty preference by affecting brain structures mediating these behaviors. We examined how EE affects features of exploratory behavior during an object in place (OiP) task in adolescent rats. Between postnatal days (pnd) 21 and 36, same-sex groups of Long-Evans rats (n = 8 each) experienced 9, 1.5-h EE sessions in cages containing a variety of objects, ramps, and platforms. Age-matched controls (8 female, 8 male) were not enriched. At pnd 36, an OiP task was performed, allowing assessment of field and object exploration and preference for objects in constant or new locations. There were 3 trials, sample and 15- and 60-min delays, that took place in a gridded, 1-m square open field. Time contacting each of 4 objects present on each trial was recorded, with the locations of two objects switched before Trial 2 and of the other two objects switched before Trial 3. After testing, brain tissue was

processed to neural activity in basolateral amygdala (BLA) using c-fos as a marker. Counts from sampling frames within BLA revealed similar numbers of activated neurons in EE and control brains. Across OiP trials, EE rats explored 43% more territory of the open field ($p<.05$) and spent 58% more time in the internal portions of the field ($p<.05$) than control rats. Controls decreased time spent exploring objects in the field from Trial 1 to 3 (54-s, 32-s, 32-s), and EE rats increased time spent with objects across the same baseline, 15-min and 60-min delays (38-s, 42-s, 49-s) ($p<.01$). While EE rats spent similar proportions of time with newly located objects on both delay trials (0.53 and 0.57, both SD=0.13), controls investigated the newly placed objects more at the 15-min (M=0.67, SD=0.17) than 60-min delay (M=0.36, SD=0.23) ($p<.01$). Behavioral data suggest that EE promotes fairly complete initial exploration of all areas of a simple environment. EE also increases exploration of a familiar but rearranged space upon re-introduction to that environment in young adolescent rats. Further, EE appears to promote balanced investigation of an environment diminishing any preference for familiarly or newly located features.

Disclosures: **E.A. Artz:** None. **H.L. Johnson:** None. **S.J. Snouse:** None. **T.J. Arnold:** None. **Z.H. Richardson-Bull:** None. **S.A. Blake:** None. **M.C. Zrull:** None.

Poster

569. Adolescent Development: Animal Models

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Topic: A.09. Adolescent Development

Support: NIH MH099625 to JM Juraska

Title: Changes in the number of synapses in the medial prefrontal cortex across adolescence

Authors: *C. DRZEWIECKI, J. WILLING, J. M. JURASKA;
Univ. of Illinois, Champaign, IL

Abstract: Adolescence is marked by numerous neuroanatomical changes within the medial prefrontal cortex (mPFC), a brain region known to mediate executive function. In rats, these morphological changes include increases in white matter, as well neuron and dendritic losses between childhood and adulthood. Prior work from our laboratory has demonstrated that these neuron losses occur during the pubertal period and may be related to female sex hormones. However, less is known about the trajectory of synaptic losses across adolescence. Here, we track changes in the number of synapses labeled with synaptophysin in the male and female rat

mPFC across multiple time points from preadolescence into adulthood (P25, P30, P45, P60 and P90). Our results showed an overall significant post-pubertal drop between P35 and 45 in the number of synapses in the female mPFC. Although this pattern occurred in all of the layers, it was predominately driven by changes in layer I synapses, with a significant rise between P25 and 35. In male rats, there was a significant pre-pubertal rise in synapses between P35 and 45, followed by a post-pubertal decline between P45 and 60 in layer V/VI. This pattern also appeared over all layers but did not reach significance. As a whole, these results suggest a role for both male and female pubertal hormones in the trajectory of synaptic loss within the mPFC during adolescence. This may shed light onto why adolescents are notably susceptible to mental illnesses such as depression and schizophrenia, both of which are associated with prefrontal synaptic abnormalities.

Disclosures: C. Drzewiecki: None. **J. Willing:** None. **J.M. Juraska:** None.

Poster

569. Adolescent Development: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 569.25/A96

Topic: A.09. Adolescent Development

Title: Perinatal SSRI exposure and social behaviors in juvenile offspring

Authors: *M. HAZLETT[1], M. GEMMEL[1], E. CSÁSZÁR[1,3], S. DE LACALLE[2], J. PAWLUSKI[1,4];
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Abstract: Up to 20% of women experience depression during pregnancy or the postpartum period. Selective serotonin reuptake inhibitor (SSRI) medications are the most common antidepressant treatment for maternal mood disorders, being prescribed to up to 10% of women during this time. SSRI medications have been shown to cross the placental barrier; additionally, they are present in the breast milk of mothers taking these medications. Thus, there are concerns about the impact of SSRI exposure on offspring development. Previous research has shown a significant effect of early exposure to SSRI medications on juvenile play behavior and other aspects of social behavior; however, further work is needed to determine how perinatal exposure to SSRI medications, using a model of maternal adversity, may affect related neurodevelopmental outcomes in juvenile male and female offspring. The aim of the present

study was to examine how exposure to fluoxetine, a popular SSRI used during the perinatal period, affects social behavior in juvenile rat offspring, using a model of maternal adversity. To do this, Sprague-Dawley rat dams were subjected to chronic unpredictable stress prior to breeding and were treated with fluoxetine (10mg/kg/day) or vehicle via oral administration from gestational day 10 to postnatal day 21. Juvenile offspring from the following four groups were used: 1. Control+Vehicle, 2. Control+Fluoxetine, 3. Pregestational Maternal Stress+Vehicle, 4. Pregestational Maternal Stress+Fluoxetine. Offspring underwent a social interaction test one week after weaning. Preliminary results show that juvenile offspring perinatally exposed to fluoxetine spend less time pouncing on and crawling over or under a novel same-sex partner, as well as less time running away from a same sex partner. Further work will determine the impact of exposure to pregestational maternal stress on these outcomes as well as investigate how these changes in social behavior are related to neural plasticity in the hippocampus. Understanding the impact of perinatal exposure to SSRI medications on neurodevelopmental processes will further enhance our understanding of the benefits and risks of perinatal administration of these medications.

Disclosures: **M. Hazlett:** None. **M. Gemmel:** None. **E. Császár:** None. **S. De Lacalle:** None. **J. Pawluski:** None.

Poster

569. Adolescent Development: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 569.26/A97

Topic: A.09. Adolescent Development

Title: Perinatal ssri exposure and social behaviors in adult offspring

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Abstract: Selective serotonin reuptake inhibitor (SSRI) medications are the most frequently used antidepressant treatment for maternal mood disorders throughout pregnancy and in the postpartum period. Increased prevalence and duration of SSRI treatment, and the ability of antidepressant medications to cross the placental barrier, suggests possible impact on fetal neurobehavioral development. Furthermore, clinical research has shown that exposure to SSRIs during the perinatal period is associated with increased autistic traits in children and alterations

in social behaviors. Investigation of perinatal exposure to SSRIs and their effects on offspring brain and behavior are crucial in understanding the long-term effects of these medications on key aspects of development. The aim of this study was to determine the persisting effects of perinatal exposure to the SSRI medication, fluoxetine, on social behavior in adult offspring. Sprague-Dawley rat dams were treated during gestation until weaning with fluoxetine (10mg/kg/day), or vehicle, via oral administration. Half the dams were subject to chronic unpredictable stress prior to conception to model aspects of maternal depression during pregnancy and thus better mimic the clinical situation. Male and female offspring from the following four exposure groups were used: 1.Control+Vehicle (CV), 2.Control+Fluoxetine (CF), 3.Pregestational Maternal Stress+Vehicle (PMSV), 4.Pregestational Maternal Stress+Fluoxetine (PMSF). Play behavior in juvenile offspring and social interaction in adult offspring was assessed. In juvenile offspring, preliminary results show perinatal exposure to fluoxetine reverses the decrease in play behavior seen after exposure to dams who were pregestationally stressed. During adulthood, preliminary findings show that adult offspring perinatally exposed to fluoxetine spend more time interacting with a novel same-sex partner compared to controls. Specifically adult offspring exposed to fluoxetine spent more time performing peer-directed behaviors such as sniffing and following. In addition, adult male offspring spent more time engaging in these behaviors than adult female offspring. Further work will determine the long-term impact of exposure to pregestational maternal stress on these outcomes as well as investigate how these changes in social behavior are related to neural plasticity in the hippocampus and prefrontal cortex. Understanding the impact of perinatal exposure to SSRI medications on the neurodevelopmental processes related to social behaviors will further enhance our understanding of the benefits and risks of these medications during development.

Disclosures: **M. Gemmel:** None. **E. Csaszar:** None. **C. Vesel:** None. **S. De Lacalle:** None. **J. Pawluski:** None.

Poster

569. Adolescent Development: Animal Models

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Topic: A.09. Adolescent Development

Support: NIAAA Grant AA019767

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NIAAA Grant AA007573

NIAAA Grant AA021040

NIAAA Grant AA020023

NIAAA Grant AA020024

NIAAA Grant AA020022

Title: Magnetic resonance imaging and histology reveal adolescent binge ethanol-induced alterations in the developmental trajectory of the young adult rodent cerebral cortex

Authors: *F. T. CREWS[1], R. YAXLEY[2], B. PANIAGUA[2], A. G. JOHNSON[3], R. P. VETRENO[2];
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Abstract: Adolescence is a critical period of cortical maturation characterized by cortical expansion and thinning that parallels the development of adult behaviors. However, little is known regarding the trajectory of cortical development in the adult brain. Adolescent binge alcohol consumption is common and can exert deleterious effects on cortical refinement due to the heightened neuroplasticity that characterizes the adolescent brain. In the first series of experiments, we used magnetic resonance imaging (MRI) and histology to assess adult cortical thickness changes across aging on postnatal day (P)80 and P220 in the male Wistar rat brain. Magnetic resonance imaging revealed cortical expansion in the prefrontal cortex across aging, while cortical thinning occurred in both the cingulate and parietal cortices of adult P220 rats, relative to young adult P80 rats. In the second series of experiments, an animal model of adolescent intermittent ethanol (AIE; 5.0 g/kg, i.g., 20% ethanol w/v, 2-days on/2-days off from P25 to P55) was used to assess the effects of alcohol on the trajectory of cortical thickness refinement in young adult (P80) rats. Magnetic resonance imaging revealed that AIE treatment led to premature cortical thinning in the young adult prefrontal cortex as well as deficits in cortical thinning in the cingulate cortex, an effect that was replicated with histology. Thus, cortical refinement continues to occur throughout the aging rat brain and AIE treatment causes changes in the developmental trajectory of the young adult cortex that could contribute to behavioral dysfunction in adulthood. (Supported by the NADIA of the NIAAA)

Disclosures: F.T. Crews: None. **R. Yaxley:** None. **B. Paniagua:** None. **A.G. Johnson:** None. **R.P. Vetreno:** None.

Poster

569. Adolescent Development: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 569.28/A99

Topic: A.09. Adolescent Development

Support: DSRG Round #10, The Graduate Center, CUNY

Title: Effect of sensory enrichment on perineuronal nets recovery following prolonged sensory deprivation

Authors: *P. CHU[1,2], S. FARAH[4], S. ALI[4], A. WAHID[4], J. C. BRUMBERG[3,5];
[1]Queens College, City Univ. of New York, Flushing, NY; [2]Neuropsychology Doctoral Subprogram, [3]Neuroscience-Biology Ph.D. Subprogram, The Grad. Center, CUNY, New York City, NY; [5]Psychology, [4]Queens College, CUNY, Flushing, NY

Abstract: Perineuronal nets (PNN's) are extracellular matrix aggregates in the central nervous system that are involved with regulating plasticity and protecting inhibitory interneurons from oxiditative stress. We have previously shown that one month of sensory deprivation via whisker trimming from the day of birth (P1) to 30 postnatal days (P30) reduces PNNs which do not recover following 30 days of whisker regrowth. In the current work, we used fluorescent labeling using FITC-Wisteria Floribunda, and unbiased stereology to determine whether the effects of critical period sensory deprivation on PNNs can be reversed with environmental enrichment. Sensory deprived regrow and enriched animals were both sensory deprived from P0 to P30 via bilateral whisker trimming. Sensory deprived regrow animals were allowed to subsequently regrow their whiskers for 30 days until P60 in standard housing conditions. Sensory enriched animals were allowed to regrow their whiskers in a sensory enriched cage which was larger and contained various sensory stimuli that were alternated every two days. Our data show that PNNs are reduced across layers 4 and 2/3 of the barrel cortex following early sensory deprivation, but are rescued following 30 days of sensory enrichment relative to control and sensory deprived regrow. Our results suggest that although early sensory input is important for the normal maturation of PNNs, a subsequent period of environmental enrichment in adolescents is sufficient to rescue their normal expression in adolescents.

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Poster

569. Adolescent Development: Animal Models

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Program#/Poster#: 569.29/A100

Topic: A.09. Adolescent Development

Support: MH090091

NIH NS045195

NSF IOS-0956831

Title: Sex differences in pubertally born cells persist in adult sexually dimorphic regions

Authors: *J. L. KIM[1], M. A. MOHR[2], L. L. DONCARLOS[3], S. BREEDLOVE[2], C. L. JORDAN[2], C. L. SISK[2];
[1]Psychology, [2]Neurosci., Michigan State Univ., East Lansing, MI; [3]Cell and Mol. Physiol., Loyola Univ. Chicago, Maywood, IL

Abstract: Many sexually dimorphic brain regions regulate sex-specific behaviors that emerge during puberty. Studies in rats and hamsters have established that new cells are added to these sexually dimorphic brain regions during puberty, and that a subset of these cells differentiates into mature neurons or glia. We have shown that pubertal cytogenesis occurs in the mouse brain, but whether pubertally born cells survive long enough to differentiate into mature neurons or glia is unknown. Because previous studies indicate that new cells in the mouse brain take ~3-4 weeks to mature, the current study aimed to examine long-term survival of pubertally born cells in mice. During puberty, male and female mice were given daily injections of cell birth date marker bromodeoxyuridine (BrdU; 200 mg/kg; ip) for 21 days (P28-49). All animals were sacrificed on P60 or P90. Brains were sectioned and stained for BrdU-immunoreactive (ir) cells. Quantitative analysis of BrdU-ir cell density (# BrdU-ir cells/mm2) revealed no significant difference in BrdU-ir cell density between P60 and P90 in four regions: the posterodorsal medial amygdala (MePD) and ventrolateral subdivision of the ventromedial hypothalamus (VMHvl), both male-biased neural structures, as well as the dorsomedial subdivision of the ventrolateral hypothalamus (VMHdm) and dentate gyrus (DG), both monomorphic neural structures. Moreover, males and females had the same density of BrdU-ir cells in the DG and VMHdm at each age whereas BrdU-ir cell density in MePD was ~1.5 times higher in males than females at both P60 ($t=2.96$, $p<0.02$) and P90 ($t=5.60$, $p<0.01$). Likewise, BrdU-ir cell density in the VMHvl was ~1.4 times higher in males compared to females at both P60 ($t=3.62$, $p<0.01$) and P90 ($t=2.65$, $p<0.03$). Thus, there is long-term survival of pubertally born cells in the mouse brain, and sex differences in pubertally born cells seen in young adulthood persist for at least a month. Because new cells take longer to mature in mice compared to other rodent species, these new findings demonstrate that there is sufficient time for pubertally born cells to differentiate into mature neurons or glia and to potentially contribute to the emergence of sex-specific adult behaviors. Ongoing work includes phenotyping these pubertally born cells to determine whether they become mature neurons or glia.

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Poster

569. Adolescent Development: Animal Models

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 569.30/A101

Topic: A.09. Adolescent Development

Support: NSERC Grant

Title: Effects of testosterone on hypothalamic-pituitary-adrenal function before, during, and after puberty in male rats

Authors: ***M. GREEN**, M. MCLAREN, T. E. HODGES, C. M. MCCORMICK;
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Abstract: The hypothalamic-pituitary-adrenal (HPA) axis responds differently to stressors before puberty than it does after puberty; exposure to a stressor before puberty causes a greater and a more prolonged release of corticosterone than it does in adulthood (rev in Romeo, 2013). In experiment 1, we replicated and expanded on previous work by examining the hormonal response to acute stress before, during, and after puberty in intact male rats (postnatal days 35, 45, and 75, respectively). In response to 30 mins of restraint stress, plasma concentrations of corticosterone and progesterone increased significantly, and this increase was more pronounced at PND 35 and 45 compared to PND 75. At baseline, testosterone concentrations were higher at PND 45 and 75 than at PND 35. In experiment 2, we investigated the effects of testosterone on HPA function at each of the three ages given that testosterone concentrations are low before puberty and testosterone is known to dampen HPA activity in adulthood but not pre-pubertally (Romeo et al., 2004). At PND 30, 40, or 70 male rats were orchiectomized (OCX) and given an implant (s.c.) that contained testosterone or was left empty. Five days after surgery rats were sacrificed directly from the home-cage (baseline), after 30 mins of restraint stress, or 45 mins after termination of the stressor to examine hormone concentrations in plasma as well as AVP and Fos-ir in the PVN of the hypothalamus. In response to restraint stress, testosterone tended to dampen corticosterone concentrations in adults (PND 75), but increased concentrations at puberty (PND 45) and had no effect on concentrations before puberty (PND 35). Among OCX rats that received testosterone replacement, stress-induced corticosterone was higher at PND 35 and 45 compared to PND 75, whereas among those without replacement, concentrations were higher at PND 35 compared to at PND 45 and 75. AVP-ir was dampened by testosterone and

Fos-ir was elevated after restraint stress, but these effects were consistent across all age groups. Thus, there is evidence of testosterone regulation of the HPA axis at all three ages, but in an age-specific manner. We are currently conducting studies to examine the potential targets of testosterone's actions at each age as well as examining glucocorticoid receptor signaling to try to explain the underlying cause of age-differences.

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Poster

570. Adolescent Development: Human Imaging

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: A.09. Adolescent Development

Support: NIH/NIAAA 1R01AA019983-01

NIH/NIAAA 3R01AA019983-02S1

NIH/NCATS 1KL2RR031974-01

NIH/NICHD 2P30HD040677-11

Title: Dietary DHA and the neural bases of risk taking: Implications for substance abuse

Authors: *V. L. DARCEY[1,2], B. W. STEVENS[1], M. F. AVALOS[2], M. JAWDAT[2], E. J. ROSE[3], D. H. FISHBEIN[3], J. W. VANMETER[2];
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Abstract: The omega-3 fatty acid docosohexaenoic acid (DHA) is critical to neuronal function (Mitchell et al., 1998). Evidence supports its role the development of the prefrontal cortex (McNamara et al., 2010), a region implicated in both impulse control and regulating striatially-driven risk taking behavior. Previous research demonstrates low DHA status is related to impulsivity (e.g. Burgess et al., 2000; Conklin et al., 2007), however it is unknown whether DHA status is related to risk taking behavior. Thus, we sought to determine the relationship between DHA intake, risk taking, and the neural bases of risky decisions in drug and alcohol

naïve adolescents. Participants (N=81; age 12.6±0.8 y; 51% female) enrolled in a prospective longitudinal neuroimaging study of the risk for alcohol initiation and escalation (the Adolescent Development Study) completed a Harvard Food Frequency Questionnaire. Since long chain polyunsaturates compete for position within neuronal membranes, we examined the ratio of DHA to arachidonic acid (AA) (DHA:AA). Participants were ranked based on DHA:AA ratio and split into quartiles. We considered differences between highest ratio (HD; DHA:AA= 1.25±0.40 mg; N=21; age 12.6±0.8 y, 52.4% female) and lowest ratio (LD; DHA:AA = 0.07±0.07, N=20; age 12.8±0.9 y, 55.0% female). Groups were not different in race, socioeconomic status, pubertal stage, BMI, or IQ. Risk taking was assessed using the Wheel of Fortune game (Ernst et al., 2004) performed during functional MRI (3T BOLD EPI). Participants tried to maximize hypothetical monetary earnings over 99 total trials by choosing either a high risk/high reward or low risk/low reward (90%/10% risk paying out $9/$1, $18/$2 and 70%/30% risk paying out $7/$3, $21/$9). There were no significant behavioral differences between groups. In contrast, fMRI analyses focused on high > low risk selections revealed the LD group had greater BOLD activity in bilateral orbitofrontal cortex, right posterior cingulate cortex, and left temporoparietal junction (p_{uncorr} 0.001, cluster extent > $10mm^3$) compared to HD. There were no clusters where the opposite was true (i.e. HD > LD). These preliminary results suggest low DHA:AA intake is associated with heightened neural activation during risk taking in interconnected regions implicated in value- and risk-based decisions (Jarbo & Verstynen, 2015; Rodrigo et al. 2014). Low DHA status augments sensitivity to drug reward in rodents (Levant et al. 2004). Results suggest that adolescents with low DHA intake may exhibit heightened sensitivity to risk taking, which coupled with heightened reward sensitivity, may exacerbate later risk of drug and alcohol use.

Disclosures: **V.L. Darcey:** None. **B.W. Stevens:** None. **M.F. Avalos:** None. **M. Jawdat:** None. **E.J. Rose:** None. **D.H. Fishbein:** None. **J.W. VanMeter:** None.

Poster

570. Adolescent Development: Human Imaging

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: A.09. Adolescent Development

Support: NIH/NIAAA 1R01AA019983-01

NIH/NIAAA 3R01AA019983-02S1

NIH/NCATS 1KL2RR031974-01

NIH/NICHD 2P30HD040677-11

Title: Prenatal stress exposure is associated with altered parietal gray matter volume in healthy adolescents

Authors: *M. AVALOS[1], V. L. DARCEY[1], B. W. STEVENS[1], E. J. ROSE[2], J. VANMETER[1], D. H. FISHBEIN[2];
[1]Ctr. for Functional and Mol. Imaging, Georgetown Univ. Med. Ctr., Washington, DC; [2]Ctr. for Translational Res. on Adversity, Neurodevelopment and Substance abuse (C-TRANS), Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Prenatal stress exposure (PSE) predicts several adverse outcomes, including working memory deficits (Entringer et al., 2009), impulsivity (Van den Bergh et al., 2005), symptoms of ADHD (Rodriguez & Bohlin, 2005), and decreased gray matter density in regions including the prefrontal cortex (Buss et al., 2010). As a region developing during adolescence and associated with impulsivity and addiction (Chambers et al., 2003), it is critical to explore how PSE may affect its development. We investigated the relationship between PSE, emotion regulation and gray matter volume (GMV) in a subset of healthy, drug/alcohol naïve adolescents (age 12.3±0.4 years) enrolled in the Adolescent Development Study, a prospective longitudinal neuroimaging study of alcohol initiation and escalation. PSE was measured using a questionnaire completed by biological mothers (N=117) assessing traumatic events such as relationship conflicts or death of someone close (Entringer et al., 2009). Those with in-utero tobacco use were excluded (n=5). Participants whose mothers experienced ≥ 1 traumatic events (Trauma; N= 29) were age-matched to those who reported 0 events (No-Trauma; N=38). Groups were similar in gender, race and intelligence (Trauma: 55.1% male, 55.1% Caucasian, IQ: 107.9±15.9; No-Trauma: 39.4% male, 60.5% Caucasian, IQ: 110.8±16.6). A T1-weighted (voxel size = 1mm3) MPRAGE was acquired on a Siemens 3T scanner. Independent raters verified image quality (ICC=0.91). GMV was assessed using VBM performed in SPM8. Statistical modeling compared the 2 groups and included gender as a covariate of no interest; multiple comparisons were addressed using Non-Stationary Cluster Correction. Affective function in adolescents was measured using a parental measure of emotional control (BRIEF) and an emotional counting Stroop task. Despite no behavioral differences in emotion regulation, whole brain analysis revealed greater GMV in the Trauma group in a cluster spanning the right superior and inferior parietal cortex (1470 voxels, p=0.026, peak 44, -43, 55). This region is implicated in empathetic judgments (Silani et al., 2013) and increased GMV here is associated with antisocial behavior (Aoki et al., 2014) and mood disorders (Adleman et al., 2012). Our preliminary findings suggest that PSE may be a factor contributing to long-term neurodevelopmental changes related to the ability to process emotions. The differences in GMV may at this relatively young age-range be a precursor of future behavioral manifestations of emotional reactivity that as of yet has not been identified in our Trauma cohort and possible future risk for addiction during adolescence (Steinberg, 2005).

Disclosures: **M. Avalos:** None. **V.L. Darcey:** None. **B.W. Stevens:** None. **E.J. Rose:** None. **J. VanMeter:** None. **D.H. Fishbein:** None.

Poster

570. Adolescent Development: Human Imaging

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: A.09. Adolescent Development

Support: NIH/NIAAA 1R01AA019983-01

NIH/NIAAA 3R01AA019983-02S1

NIH/NCATS 1KL2RR031974-01

NIH/NICHD 2P30HD040677-11

CAPES 99999.004600/2014-02

Title: Associations between exposure to alcohol advertising and limbic-frontal activations during an Emotional Counting Stroop task in female adolescents at risk for alcohol misuse

Authors: *K. R. VIACAVA[1], B. W. STEVENS[2], I. M. PACHECO-COLON[2], T. N. CLARKE[2], D. MAYS[2], L. BIZARRO[3], D. H. FISHBEIN[4], J. W. VANMETER[2];
[1]Inst. of Psychology, UFRGS and Georgetown Univ., Washington, DC; [2]Georgetown Univ., Washington, DC, DC; [3]UFRGS, Porto Alegre, Brazil; [4]Univ. of Maryland, College Park, MD

Abstract: Exposure to alcohol advertising (AAds) is a risk factor for underage drinking (Fleming et al., 2004) as exposure to AAds increases the likelihood adolescents start drinking (Morgenstern et al., 2011) and predicts increased intake among alcohol consumers (Grenard et al., 2013). This study examined the relationship between AAds exposure and attentional bias (AB) for alcohol-related and emotional negative words during fMRI in female adolescents considered high risk for alcohol misuse. Participants were part of the Adolescent Development Study (ADS), a longitudinal neuroimaging study of alcohol initiation and escalation. A subset of 114 adolescents enrolled in the ADS performed an Emotional Counting Stroop (ecStroop) task during fMRI. Thirteen participants from this sample (mean age = 14.8 yrs.) completed the Media Exposure Questionnaire (MEQ; Collins et al., 2007). We performed whole brain fMRI analyses regressing the MEQ scores separately for emotional>neutral and alcohol>neutral, with results reported at $p < .001$ uncorrected. Lastly, we examined neuronal activations from the subjects not

included in this analysis (N = 101) to obtain a bias free set of region(s) of interest (ROIs) to determine whether AAds exposure mediates the relationship between neural activation and AB. Behavioral results revealed a main effect of ecStroop $F(2,24) = 15.999$, $p < .001$, and the Bonferroni post-hoc confirmed the difference between negative and neutral ($p = .002$) and between alcohol and neutral words ($p = .001$). There was a positive correlation between exposure to AAds on TV and AB for emotional negative words such that subjects exposed to AAds on sports ($r = .63$, $p = .02$) or non-sports TV channels ($r = .56$, $p = .04$) are more distracted by these words. fMRI results for alcohol>neutral showed a positive correlation between exposure to AAds and activity in limbic and frontal areas, suggesting higher exposure may be associated with greater AB for alcohol words. There was a negative correlation between exposure and fMRI activation in the orbitofrontal cortex for alcohol>neutral, which may reflect habituation to repeated AAds exposure. From the fMRI ROI's extracted, linear regression revealed the right inferior and medial frontal gyri for alcohol>neutral predicted AB for alcohol-related words ($B = .652$, $p = .03$). However, no mediation effects of exposure to AAds were found. For emotional>neutral, there was a negative correlation between AAds exposure and the insula and cingulate gyrus, implying lower emotional interference on those with higher AAds exposure. Altogether, these findings have implications for identifying risk factors for future alcohol misuse in female adolescents.

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Poster

570. Adolescent Development: Human Imaging

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Program#/Poster#: 570.04/A105

Topic: A.09. Adolescent Development

Support: 5R01AA019983-03

Title: Cortical and subcortical structural variability in drug naïve adolescents predicts subsequent alcohol use

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Abstract: Clinical models of alcohol misuse suggest a neurological profile characterized by dysfunction in multiple behavioral, cognitive and affective brain systems and abnormalities in the structures that support them. Yet, it remains to be established whether structural variability is an antecedent to or consequence of alcohol abuse. Moreover, although adolescence is seen as a period of heightened risk for alcohol use, to-date there has been no prospective exploration of the relationship between alcohol use onset in youth and variability in brain structure predating use. Here we considered aspects of brain structure (i.e. cortical thickness (CT), surface area (SA) and subcortical volume (SV)) in drug and alcohol naïve children (age 11-13 years) and their relationship to subsequent alcohol use in an 18 month follow up period. Individuals were recruited to a prospective, longitudinal study of neurodevelopmental trajectories in children at variable risk for alcohol misuse. The sub-sample in the current analysis (N=70; 41 female; mean age = 12.8 years) included 11 children who reported using alcohol at the 18 month study follow-up and 59 who remained alcohol naive. Distributions for gender, risk status and family history of substance abuse were matched between users and non-users ($p<0.05$). High-resolution T1-MPRGAGE images (voxel=1mm3) were collected in a Siemens TIM Trio 3T scanner. These scans were rated for quality and ratings were confirmed by independent raters. Data were preprocessed in Freesurfer using standard parameters and QC included visual inspection of cortical and subcortical segmentations and surface accuracy for white matter and pial surfaces. Data analysis consisted of general linear models, modeling differences between users and nonusers in CT, and SA and SV regions of interest. Covariates included total intracranial volume, gender and risk status. These analyses indicated that estimates of CT in the left cuneus and entorhinal cortex and SA in the left caudal middle frontal gyrus, right inferior temporal gyrus and right lateral occipital gyrus were all greater in users, compared to non-users. Similarly, users exhibited greater gray matter (GM) volume in the left putamen and right nucleus accumbens (NAcc). In light of other studies showing that increased GM in reward relevant areas is predictive of reward sensitivity, greater GM volume in the key reward regions (i.e., the putamen and NAcc) may suggest heightened reward sensitivity in those with a propensity to use alcohol in adolescence. While intriguing, these outcomes require replication in an extended sample and a determination of the functional and behavioral correlates of structural outcomes.

Disclosures: E.J. Rose: None. **V. Darcey:** None. **T. Clarke:** None. **D. Estefan:** None. **J. VanMeter:** None. **D. Fishbein:** None.

Poster

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NIH/NCATS 1KL2RR031974-01

NIH/NICHD 2P30HD040677-11

Title: Reductions in prefrontal cortex grey matter predict later initiation of alcohol use during adolescence

Authors: *B. W. STEVENS[1], V. L. DARCEY[1], T. N. CLARKE[1], D. L. ESTEFAN[1], E. J. ROSE[2], J. W. VANMETER[1], D. H. FISHBEIN[2];
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Abstract: In a longitudinal study of neurodevelopmental precursors and consequences of alcohol misuse (i.e., the Adolescent Development Study) we used voxel-based morphometry (VBM) to consider the relationship between grey matter (GM) volume in drug and alcohol naïve adolescents (11-13 years old) and the subsequent initiation of alcohol use. At an 18 month follow up 12 adolescents (66% female) had initiated alcohol use. Alcohol users were matched for gender, race, SES and IQ with 12 adolescents who had not initiated alcohol or drug use. High resolution (voxel size=1mm^3) structural MRI scans (MPRAGE, 3T) from baseline visits were used for VBM analysis, which was carried out using the DARTEL toolbox in SPM8. Images were segmented into GM, white matter and CSF. A study specific template was used to co-register the GM images. Statistical models also included total intracranial brain volume and gender. Correction for multiple comparisons utilized the Non-Stationary Cluster Correction plugin and data were thresholded at an uncorrected $p \leq 0.005$ and minimum cluster size (K_E) of 50 voxels. In addition to imaging measures, we also considered whether the groups differed on baseline executive function measures using the Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000). At baseline there were no behavioral differences between groups, yet participants who went on to drink alcohol by 18 months had reduced GM volume in clusters spanning the left middle and inferior frontal gyri (corrected $p = 0.043$, $K_E = 8821$) and right middle and superior frontal gyri (corrected $p = 0.066$, $K_E = 7018$). These PFC regions are well known to be associated with many functions such as working memory and inhibitory control (Collette et al., 2006; Simmonds et al., 2008), and while we found no behavioral executive function differences, possibly due to a lack of power resulting from the small number of adolescents that have begun to use alcohol, it is possible those that initiated alcohol use had baseline reductions in executive function. In addition, reduced PFC GM volume has been observed in alcohol naïve individuals with a family history of alcohol abuse (Benegal et al.,

2007). The current study extends these findings, suggesting such reductions in GM volume can serve as a risk factor predisposing individuals to initiate alcohol use.

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Poster

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NIH Grant K99/R00 MH091238

Title: Weaker baseline fronto-amygdalar resting state functional connectivity in healthy adolescents who escalate in depression symptoms over time

Authors: *H. E. STEIN[1], G. ALARCÓN[2], D. V. DEMETER[2], E. EARL[2], D. FAIR[3], B. NAGEL[3];
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Abstract: Depression is a prominent mental health concern, with greater risk associated with child and adolescent onset. Emotional dysregulation is a key feature of depression. Previous work has shown aberrant resting state functional connectivity of the amygdala in depressed adolescents, compared with healthy controls, which may be a neural substrate of altered emotional processing. While these findings suggest abnormalities in the functional connectivity of the limbic system in depressed adolescents, no studies have examined whether these abnormalities may precede depressive symptom expression. This study used resting state functional connectivity magnetic resonance imaging (rs-fcMRI) to prospectively examine potential neurobiological markers of escalating depression symptom severity in an adolescent sample (n=37, female=21, ages 12-16 years and free from psychopathology at baseline). Of these 37 participants, 18 showed ≥ one standard deviation increase in depression t-scores over time, as assessed by the Children's Depression Inventory (CDI), administered at quarterly follow-up

interviews. These 18 youth were compared to 19 youth who showed stable CDI scores over time, matched on baseline CDI scores, age, sex, IQ, and baseline alcohol and drug use. Whole-brain analyses were conducted on baseline rs-fcMRI data (≥5 min. of data after motion scrubbing; collected with eyes open), using an atlas-based seed region-of-interest (ROI) that encompassed the whole amygdala bilaterally. Functional connectivity maps were compared with a two sample *t*-test assuming unequal variance ($Z>2.25$, $p<0.05$). Results indicated that those youth who demonstrated stable CDI score over time had increased rs-fc, relative to those whose CDI scores escalated, between the right amygdala and left inferior frontal and supramarginal gyrus and right cingulate cortex. Additionally, relative to youth who showed an escalation of self-reported depression symptoms, those with stable symptom presentations had decreased rs-fc between the left amygdala and the left cerebellar vermis. These findings suggest a possible neurobiological marker of increasing depressive symptoms during adolescence, characterized in part by reduced fronto-amygdalar connectivity, which may suggest a premorbid deficiency in top-down emotional regulation.

Disclosures: H.E. Stein: None. **G. Alarcón:** None. **D.V. Demeter:** None. **E. Earl:** None. **D. Fair:** None. **B. Nagel:** None.

Poster

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Topic: A.09. Adolescent Development

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Title: EEG correlation in institutionalized adolescents: long term impact of adverse rearing

Authors: *J. C. HEVIA[1], A. SANZ-MARTÍN[2], M. GUEVARA[3], M. HERNÁNDEZ-GONZÁLEZ[4];
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Abstract: In 1989 United Nations Convention of the Rights of the Child, pronounced that every child should group up in a family environment of trust, happiness and understanding. However, not every child has the opportunity to rise on this ideal family context. It has been showed that children grown up in institutional environments, where the quality of care presents some

deficiencies, manifest a deficient development of different brain areas. There is strong scientific evidence that support that while more time spent in institutional environment, more deficiency in the development of neuronal substrates children presents, mainly the prefrontal cortex. In this work was measured the electroencephalographic (EEG) correlation between prefrontal, temporal and parietal areas in 10 adolescents institutionalized that had lived in institutional environment since preschooler ages (more than 75% of their life time) and 10 that never had lived institutionalized. A higher EEG correlation between interhemispheric frontopolar areas and between intrahemispheric frontopolar-dorsolateral areas in slow bands of institutionalized adolescents was observed. Besides, a higher intrahemispheric EEG correlation between left dorsolateral-parietal areas in fast frequency bands was also obtained in never institutionalized children. These EEG changes shown that growing up in a institutional environment affect the degree of EEG coupling among cortices.

Disclosures: J.C. Hevia: None. **A. Sanz-Martín:** None. **M. Guevara:** None. **M. Hernández-González:** None.

Poster

570. Adolescent Development: Human Imaging

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Program#/Poster#: 570.08/B1

Topic: A.09. Adolescent Development

Title: Assessment of impulsivity, inhibitory control and alcohol use in preadolescents and adolescents: students from five schools in Porto Alegre, Brazil

Authors: *A. R. WILLHELM, J. C. C. CABRAL, L. M. UGARTE, R. M. M. DE ALMEIDA; Inst. de Psicologia, Univ. Federal Do Rio Grande Do Sul, Porto Alegre, Brazil

Abstract: The periods of preadolescence and adolescence are characterized by maturation of emotional and cognitive skills that provide capabilities to the independent functioning in adulthood. The last area to develop in the central nervous system is the prefrontal cortex, the area also linked to the ability to control impulses, this suggests that preadolescents have less ability to control than adolescents and adolescents have less ability to inhibitory control than adults. The consumption of licit and illicit drugs are increasingly present in the lives of adolescents. The main aim was evaluate impulsivity, inhibitory control and alcohol use in preadolescents and adolescents age 10 to 16. The specific objectives were to compare impulsivity and inhibitory control among boys and girls and between three age groups (from 10 to 12, 13 and 14 years and 15 to 16 years old). The sample was composed for 190 individuals age 10 to 16, divide in three

age groups (from 10 to 12, composed of 52 participants, 13 and 14 years with 49 participants and 15 to 16 years with 89 participants) from private and public schools. The instruments used were: Questionário de Capacidades e Dificuldades, Questionário sobre o início do uso de drogas, Barratt impulsiveness scale-youth, Go/No-go task, Five Digits test e Escala de Inteligência Wechsler Abreviada (WASI). Statistically significant differences were observed ($p < 0,01$) in performance between the three age groups, showing a chronological increase in inhibitory control. For comparisons between types of school were significant statistical differences at all times of the task Go/No-go ($p < 0,05$) and in some subtests of the Five Digits Test, the better performance of students in private schools. Comparing the sexes was statistically significant difference of which variable, indicating a lower inhibitory control female. Approximately 60% of adolescents have tried alcohol and 17% with illicit drugs. It was observed that preadolescents are consuming alcohol ever earlier and in greater quantity. We can conclude that control the ability to inhibit increases through adolescence. In addition, public school students showed worse performance in inhibitory control and greater impulsivity, and it was suggested that perhaps the environment are related with this performance. Girls showed less inhibitory control than boys, committing more errors of omission in the Go/No-go task, suggesting that the sample, girls have higher attentional impulsivity than boys.

Disclosures: **A.R. Willhelm:** None. **J.C.C. Cabral:** None. **L.M. Ugarte:** None. **R.M.M. de Almeida:** None.

Poster

570. Adolescent Development: Human Imaging

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Topic: A.09. Adolescent Development

Support: R01 AA017664 (Nagel)

T32 AA007468 (Phillips)

Title: Longitudinal sex differences in brain activity during spatial working memory in adolescents

Authors: *S. A. JONES[1], B. J. NAGEL[2];
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Abstract: It is well established that adolescence is a time of numerous structural and functional changes in the brain, many of which may differ by sex. To that end, prior studies have documented sex differences in brain response during spatial working memory (SWM) across adolescence. However, to date, most of these findings have been observed using a cross-sectional design, which may not account for individual variability or accurately reveal developmental findings. The current study used functional magnetic resonance imaging to longitudinally investigate development and sex differences in brain response to SWM using an n-back task in healthy female (n=16) and male (n=16) adolescents (ages 12-16 at baseline). All participants underwent two scans, separated by a mean of 1.5 years (SD=0.67). Whole-brain repeated-measures ANOVA, examining main effects of sex, time, and their interaction, revealed that during SWM, at both time points, males showed significantly greater brain activation in task-related regions, such as the bilateral inferior parietal lobule (IPL) and lingual gyrus, as well as default mode network regions, such as precuneus and posterior cingulate cortex (voxel/cluster-wise corrected for multiple comparisons, $p<.05$). However, there were no regions that showed a significant developmental effect (main effect of time), or sex-by-time interaction. To investigate the possibility of non-linear developmental trends masked by the broad baseline age-range of the sample, we split the sample based on median age at baseline (14.8 years) to examine these effects in younger and older adolescents, separately. Again, repeated-measures ANOVAs found no significant main effect of time or sex-by-time interaction in either group; however, similar sex differences as those seen across the whole sample were evident in the left IPL in younger adolescents and in the precuneus and lingual gyrus in older adolescents, again with males showing greater activation than females in both age groups. These results suggest that compared to females, males require greater activation of task-related regions during SWM and may have greater difficulty suppressing default mode regions during the task, with the latter appearing particularly evident later in adolescence. These findings highlight the importance of considering sex differences in SWM-related brain response and suggest that a broader age range with multiple scans within-subject may be necessary to elucidate developmental effects longitudinally.

Disclosures: S.A. Jones: None. **B.J. Nagel:** None.

Poster

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Topic: A.09. Adolescent Development

Support: K01 MH102609

R01 MH099156

P41 EB015893

Title: *In vivo* mapping of cortical glutamate in early youth

Authors: *D. R. ROALF[1], M. QUARMLEY[2], R. REDDY NANGA[3], P. RUPERT[2], H. HARIHARAN[3], K. RUPAREL[2], J. BLAKE[2], M. A. ELIIOTT[3], R. REDDY[3], B. I. TURETSKY[2];
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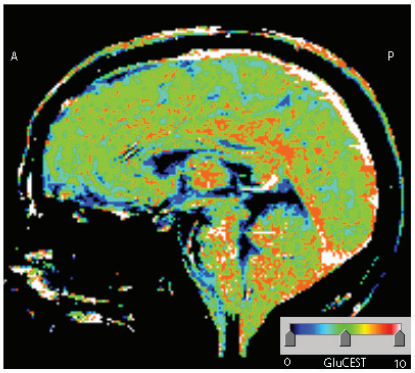
Abstract:



The cortex undergoes a protracted course of post-natal development during childhood and through young adulthood. In addition to allowing for expanded area, the brain's gyral structure allows enhanced computational efficiency within the gyral unit by speeding local information transfer and reducing wiring cost. In addition to progressive brain tissue changes, developmental changes in neurotransmitter availability likely precede or underlie these cortical changes. Here, we use a novel technique glutamate chemical exchange saturation transfer (GluCEST) to measure glutamate concentration, *in vivo*, across the entire cortex. We implemented an optimized

within-subject acquisition and analysis pipeline. Upon completion of 3T MRI scanning, each subject's whole-head structural image were segmented using FreeSurfer and ROIS were extracted and prepared for use with GluCEST data acquired at 7.0T. GluCEST, B0 map and B1 maps were collected and analyzed (Figure, from one individual). GluCEST data from 25 young healthy individuals and 25 individuals with clinical psychopathology were acquired. Our preliminary work indicates subtle, but significant changes in the distribution of GluCEST throughout the cerebrum that changes in a regionally dependent manner with age. In addition, the distribution of glutamate differed between the clinical sample and young healthy individuals (ps<.05). We suggest, that in addition to other metrics, GluCEST be considered as markers of brain development. Moreover, we believe that high-resolution GluCEST MRI could help elucidate subtle features of normal and abnormal brain. For example, hyperglutamatergic states within the brain are associated with schizophrenia and may aid in identifying individuals at risk for this disorder. Thus, the use of 7.0T GluCEST to map glutamate may yield improved quantification of brain neurochemistry and could improve diagnosis of brain disorders associated with alterations in glutamate.

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Poster

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Topic: A.09. Adolescent Development

Support: ERC-StG-2012-313749

Title: Neural control of social emotional actions in adolescence

Authors: *A. TYBOROWSKA[1,2], I. VOLMAN[1,2,3], S. SMEEKENS[2], I. TONI[1], K. ROELOFS[1,2];
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Abstract: Increased limbic and striatal activation in adolescence has been attributed to a relative delay in the maturation of prefrontal areas, resulting in the increase of impulsive reward-seeking

behaviors often observed during puberty. However, it remains unclear whether and how this general developmental pattern translates to the control of social emotional actions, a fundamental adult skill refined during adolescence. Using an fMRI-adapted social Approach-Avoidance (AA) Task, this study identifies how neural properties of emotional action control change as a function of pubertal development in 14-year-old adolescents (n=47; 21 males). During the AA-Task, participants had to evaluate the emotional expression (happy, angry) of faces and respond by either pulling a joystick toward (approach) or away (avoidance) from themselves. Affect-congruent conditions involved intuitive stimulus-response mappings (i.e. approach-happy and avoid-angry faces). In contrast, affect-incongruent conditions required participants to override these emotional action tendencies in order to meet task demands (i.e. approach-angry and avoid-happy faces). Pubertal maturation, indexed by testosterone levels, shifted the neural regulation of emotional actions from the pulvinar nucleus of the thalamus and the amygdala to the anterior prefrontal cortex (aPFC). Adolescents with more advanced pubertal maturation showed greater aPFC activity when controlling their emotional action tendencies, reproducing the same pattern previously observed in adults. In contrast, adolescents with less advanced pubertal maturation showed greater pulvinar and amygdala activity when exerting the same amount of control. These findings qualify the generic notion of a shift from subcortical to prefrontal processing during puberty, suggesting that the pulvinar and the amygdala are the ontogenetic precursors of the mature emotional control system centered on the anterior prefrontal cortex. The maturational shift of subcortical - prefrontal control is hypothesised to transition by late adolescence. We are currently testing this possibility by sampling the same participants later in their pubertal maturation.

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Poster

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Topic: A.09. Adolescent Development

Support: U01 AA017122

F32AA022561

F32HD078084

Title: Associations between white matter microstructure and gonadal hormone levels are altered in youth with fetal alcohol spectrum disorders (FASD)

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[3]USC, Los Angeles, CA

Abstract: In animal models, prenatal alcohol exposure (PAE) results in endocrine dysregulation and sexually dimorphic brain alterations. However, very little is known about sex differences and hormone levels among youth with Fetal Alcohol Spectrum Disorder (FASD). The present study aimed to begin to fill this gap using diffusion tensor imaging (DTI) to assess how gonadal hormones relate to white matter microstructure in PAE youth. DTI measures restriction of water diffusion known as fractional anisotropy (FA). Previous studies suggest that PAE results in decreased FA, which may underlie common cognitive and behavioral deficits. Thus, we hypothesized that PAE would be associated with reduced FA, and hormone-FA associations would be altered by PAE in a sexually dimorphic manner. Sixty-one youth (8-20 yrs; 49% girls; 50% PAE) participated as part of the Collaborative Initiative on FASD (CIFASD). Participants completed a 30 directional DTI scan and a passive drool sample to examine FA-hormone associations with Testosterone (T), dehydroepiandrosterone (DHEA), and estradiol (E2). After standard preprocessing and motion correction, FSL's tract-based spatial statistics program was utilized to generate mean FA for 9 regions of interest (ROIs). In R, Group x Age interactions were analyzed separately for boys and girls, using linear regression for unilateral ROIs, and linear mixed effect modeling, including hemisphere, for bilateral ROIs. Compared to Control youth, FASD girls exhibited lower FA values in inferior fronto-occipital (IFO) and uncinate white matter tracts, but FASD boys exhibited higher FA values in the callosal body, cingulum, corticospinal, optic radiation and superior longitudinal fasciculus (SLF) white matter tracts (p's<0.05). These novel findings demonstrate sexually dimorphic effects of PAE on structural connectivity in youth. Positive associations between T and DHEA with FA were observed with the callosal body, optic radiation, and SLF in Control boys, but only with the SLF in FASD boys (p's$<.10$). A positive E2-FA association was observed with the IFO among Control girls ($p<.10$), while no hormone-FA associations were observed among FASD girls (p's$>.32$). These novel findings provide evidence that PAE results in a loss of typical hormone-FA associations observed among Control youth, particularly among boys with FASD. Importantly, the present results have implications for understanding sex differences in how PAE impacts hormone-brain associations, which may have implications for advancing our understanding of common cognitive, behavioral and mental health problems that occur at a high prevalence among individuals with an FASD.

Disclosures: K.A. Uban: None. **M.M. Herting:** None. **J.R. Wozniak:** None. **E.R. Sowell:** None.

Poster

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Topic: A.09. Adolescent Development

Title: During the puberty morphological differences in autism are due to increased gyrification

Authors: *R. SIUGZDAITE, H. AERTS, D. MARINAZZO;
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Abstract: Social communication (SC) can be defined as "the synergistic emergence of social interaction, social cognition, pragmatics (verbal and nonverbal), and receptive and expressive language processing" (Adams, 2005). SC disorder can include problems with one or all the three components: social interaction, social cognition and pragmatics. To assess the disorder a lot of behavioral testings are performed including IQ, Social responsiveness scale (SRS), Social communication questionnaire (SCQ) and ect. But can we detect SC disorder from the structural differences in the brain between groups? Previous studies (Libero et al 2014, Valk et al 2015, Wallace et al 2013) showed distributed abnormalities in frontal and temporal brain areas. Inconsistencies come from different age groups and sample sizes (small groups within a specific age group or a huge heterogeneous age group), though in both cases the results were pointing to regions involved in social cognition. In this study we have picked age specific group of 103 children with ASD and 103 TD controls from the Autism Brain Imaging Data Exchange open-access database matched for age (average 10.5 ± 1.6 years). Groups were significantly different in social communication measures (VIQ, SRS and SCQ scores). We performed surface based morphological analysis using FreeSurfer (Fischl, 2012) to find properties of cortical regions involved in social communication disturbancies in children with autism spectrum disorder. We didn't find any grey matter differences in cortical volume or surface area between groups, but left inferior lateral ventricle and right choroid plexus were bigger in ASD than in controls. We also found smaller cortical thickness in left parahippocampal and in right middle frontal regions in ASD. Finally, folding measurements revealed differences in left hemisphere (fusiform, middle temporal areas, rostral middle frontal and lateral occipital gyri). We conclude that at age of puberty children brains do not differ in volume or surface area, though the only difference involves curvature of gyri, the way they are formed during the development of the brain. The gyrification in left rostral middle frontal area correlates with ADOS social scores and this could be a potential biomarker for social communication in ASD.

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Poster

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Wellcome Trust Strategic Award 095844/Z/11/Z

MRC Grant MR/K020706/1

Title: Similar maturational trajectories of functional modules in human adolescent brain networks

Authors: ***F. VÁŠA**[1], P. E. VÉRTES[1], K. J. WHITAKER[1], R. ROMERO-GARCIA[1], A. ALEXANDER-BLOCH[2,3], P. KUNDU[4], A. X. PATEL[1], R. TAIT[1], C. OOI[1], J. SUCKLING[1], B. INKSTER[1], P. FONAGY[5], R. DOLAN[6], P. B. JONES[1], I. GOODYER[1], E. BULLMORE[1,7,8]; [1]Psychiatry, Univ. of Cambridge, Cambridge, United Kingdom; [2]Child Psychiatry, Natl. Inst. of Mental Hlth., Bethesda, MD; [3]David Geffen Sch. of Med., UCLA, Los Angeles, CA; [4]Psychiatry, The Mount Sinai Hosp., New York City, NY; [5]Psychology, [6]Neurol., Univ. Col. London, London, United Kingdom; [7]Clin. Unit Cambridge, Glaxo-Smith Kline, Cambridge, United Kingdom; [8]Cambridgeshire and Peterborough NHS Fndn. Trust, Cambridge, United Kingdom

Abstract: Although numerous psychiatric disorders emerge as a result of abnormal brain development in adolescence, our understanding of normative maturation during this period remains limited. We apply the complex network framework to study the relationship between developmental trajectories of functional connectivity (FC) from 14 to 25 years and the architecture of FC in young adulthood. Anatomical and functional 3T scans were acquired from 97 healthy volunteers aged 14-25 (49M / 48F). The fMRI signal was de-noised using multi-echo ICA [1] and averaged over 272 cortical regions of interest. For each participant, weighted graphs were estimated where each node is a brain region and links correspond to correlations in fMRI signal. Nodal connectivity strength was calculated as the sum of the weights of each node's links to all other network nodes. The cross-sectional development of local strength as a smooth function of age was assessed using a generalized additive model. Pair-wise differences in

regional developmental trajectories were estimated by integrating over differences between the first derivatives of the smooth functions, and clustered using k-medoids clustering. An average adult FC matrix was created from subjects aged 22-25, which was partitioned into modules. A significant relationship between maturational similarity and adult FC was present, indicating that regions which follow more similar (less dissimilar) maturational trajectories in adolescence are more strongly connected in the adult brain. A subdivision of the maturational trajectories into five clusters yielded high overlap with a partition of adult FC into five modules. FC was significantly stronger within maturational clusters than within a set of randomized cluster partitions (preserving cluster size, spatial contiguity and hemispheric symmetry), particularly in parietal and occipital regions. Additionally, maturational trajectories were significantly more similar (less dissimilar) within FC modules than within randomized modular partitions. The strong correspondence between the adolescent maturation of functional connectivity and its architecture in the cortex of young adults could be explained by a network-level Hebbian mechanism. Such a mechanism was previously proposed to explain that resting-state networks result from the strengthening of connections due to task-based co-activations [2]. Our results provide a novel interpretation for the role of such a mechanism, indicating that high average FC between cortical regions might result from similarity in their developmental trajectories. [1] Kundu et al., PNAS 2013 [2] Sporns, Dialogues Clin. Neurosci 2013

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Poster

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KKF 8765162

Title: Birth weight predicts aberrant striatal intrinsic functional connectivity in preterm born adults

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Abstract: Background: Preterm birth constitutes a high risk for perinatal brain injury and adverse brain development. Both studies using animal models of premature delivery and neuroimaging studies in humans consistently point to the striatum as a structure to be particularly affected by preterm birth. Recently, we demonstrated aberrant intrinsic functional connectivity (iFC) of the basal ganglia network together with structural changes in underlying gray matter in preterm born young adults. Yet, little is known about the long-term consequences of preterm birth on the iFC of different striatal sub-regions at large-scale brain level. Method: Using resting-state functional magnetic resonance imaging we investigated seed-based intrinsic functional connectivity (iFC) of 12 striatal sub-regions (6 per hemisphere) in 91 preterm and 90 term born young adults (mean age 26 years). Voxel-wise statistical parametric maps quantified within-group striatal iFC and between-group differences for three caudate and three putamen seeds per hemisphere. Subsequently, prematurity-related variables (e.g. birth weight) were used to predict potential between-group iFC differences. Results: Across all subjects whole-brain voxel-wise one sample t-tests ($p<0.05$, FWE cluster corrected) for each of the 12 striatal sub-regions revealed distinct spatial maps highly consistent with the previously hypothesized sensorimotor, associative and limbic divisions among striatal sub-regions. Two sample t-tests ($p<0.05$, FWE cluster corrected) revealed that preterm born adults demonstrated a reduced iFC between ventral striatal seeds and both frontal cortex and caudate nucleus, and between dorsal striatal seeds and frontal, premotor, cingulate and insular cortices. Interestingly, between-group differences were almost exclusively found in seeds placed in the right hemisphere. Preterm born adults did not show increased iFC for any of the striatal seeds. Moreover, within the preterm group, birth weight significantly predicted the reduced iFC between the left ventral rostral putamen and the right caudate nucleus ($p<0.001$). Conclusion: Our data demonstrate the long-lasting effect of preterm birth on cortico-striatal and striatal-striatal connectivity into adulthood involving both the motor, cognitive and affective divisions among striatal sub-regions. The link between preterm born subjects' birth weight and aberrant iFC of striatal sub-regions in adulthood suggests striatal iFC to be a potential long-term biomarker of preterm birth.

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Poster

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Title: The age-effects on topological lateralization of hemispheric brain network from adolescence to adulthood

Authors: *S. ZHONG, Y. HE, G. GONG;
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Abstract: Human brain is functionally and structurally lateralized and related to cognitive development across the life span. Brain functional lateralization may result from the difference of information processing between two hemispheres. Complex network analysis and graph theoretical approach can be used to study the efficiency of the information processing within the hemisphere. Here, we aim to spatially map the maturation of topological lateralization of the structural network from adolescence to adulthood, which might provide novel insights into brain functional lateralization and its developmental patterns. 106 adolescence and 98 adults were included. We first constructed two hemispheric structural networks for each subject. Then, the topological organization was quantified by the two network metrics (i.e. global efficiency and local efficiency) and one nodal metric (nodal efficiency). The degree of asymmetry of the network metrics was measured by LI=(Mr-Ml)/(Mr+Ml) . Finally, we applied paired t-test and a linear model were used to test if there is a topological lateralization in network metrics for either adolescent or adult group and the adolescent vs. adult group differences for the LI of network metrics, separately. There was significant rightward lateralization in the global efficiency for both adolescent and adult groups, while significant rightward lateralization in the local efficiency appeared only in adolescence. A significant group main effect on the LI was observed for both the local efficiency and global efficiency. For the nodal efficiency of the adolescence, the rightward lateralization regions were mainly located in the parietal lobe, temporal cortex, frontal cortex, and lateral inferior occipital regions, while this rightward lateralization became much less, with substantial leftward lateralization being found within temporal and occipital lobes in adulthood. The significant main group effect on the LI for the nodal efficiency (FDR corrected $p<0.05$) were mainly located around the posterior temporal cortex, temporal-parietal junction,

and inferior occipital cortex. These findings might provide new insights into brain structural and functional development.

Disclosures: **S. Zhong:** None. **Y. He:** None. **G. Gong:** None.

Poster

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Topic: A.09. Adolescent Development

Title: Pubertal status-dependent differential recruitment of ventral striatum and prefrontal cortex during reward processing

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Abstract: Adolescence is a time of increased risk-taking and reward sensitivity. Current models of human brain development posit that a functional imbalance between prefrontal cortex and subcortical regions contributes to these behaviors, due to the earlier development of limbic regions compared to the more protracted development of prefrontal cortex. Despite considerable evidence that hormones affect brain structure and function, nearly all neurodevelopmental studies of reward processing define childhood and adolescence based on age alone and do not consider measures of hormonal exposure such as Tanner Stage. Fifty typically developing children and adolescents underwent Tanner staging by a clinician and performed a monetary incentive delay task in a 3T fMRI scanner. Groups were defined based on both age and Tanner stage (Pre-pubertal: N=23, average age=8.6 years, age range 8.1-9.4, all Tanner stage 1, 11 females; Pubertal: N=27, average age=13.1, age range 12.1-14.6, Tanner stages 2-5, 12 females). Whole-brain voxel-wise data for reward anticipation and reward gain were analyzed in SPM5 to compare pre-pubertal children and pubertal adolescents, with sex added as a covariate of no interest. During reward anticipation, adolescents showed significantly greater activation in right orbitofrontal cortex and basolateral amygdala than pre-pubertal children ($p<0.001$, uncorrected)

with no differences observed in the opposite direction. During reward outcome, adolescents showed greater activation in right dorsolateral prefrontal cortex (DLPFC) and medial prefrontal cortex; pre-pubertal children, in contrast, had greater activation in right ventral striatum ($p<0.001$, uncorrected). In post hoc analyses, the predominance of DLPFC over ventral striatum (DLPFC - ventral striatum) during reward outcome was found to decrease with age in the pubertal group ($R=-0.43$; $p<0.03$), but was not correlated across the relatively restricted age range in the pre-pubertal group. These data provide evidence for greater recruitment of prefrontal cortex regions in pubertal adolescents compared to pre-pubertal children, consistent with studies of structural and functional development. The division of children into pre-pubertal and pubertal by clinical examination rather than by age alone provides confirmation that these groups are developmentally distinct. The Tanner scale defines development based on external sex characteristics that are dependent on pubertal timing and typically covary with age. Future longitudinal analyses will attempt to disentangle the roles of age, Tanner stage, and reproductive steroids in development of reward processing during adolescence.

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Poster

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Topic: A.09. Adolescent Development

Title: White matter abnormalities in HIV+ children and associations with processing speed

Authors: ***A. SAREMI**[1], W. PRASITSUEBSAI[2], N. JAHANSHAD[1], T. M. NIR[1], K. CLIFFORD[3], L. AURPIBUL[4], P. M. THOMPSON[1,6], K. PRUKSAKAEW[2], S. LERDLUM[7], P. VISRUTARATNA[5], S. J. KERR[2], T. PUTHANAKIT[2,7], R. PAUL[8], J. ANANWORANICH[2,9,10], V. G. VALCOUR[3];
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Pediatrics, Engineering, Psychiatry, Radiology, & Ophthalmology, USC, Los Angeles, CA; [7]Fac. of Med., Chulalongkorn Univ. Hosp., Bangkok, Thailand; [8]Dept. of Psychology, Univ. of Missouri, St. Louis, MO; [9]Military HIV Res. Program and Henry M. Jackson Fndn. for the Advancement of Military Med., Bethesda, MD; [10]SEARCH-Thailand, Bangkok, Thailand

Abstract: Vertical transmission of the human immunodeficiency virus (HIV) from mother to child is still a major public health problem in many countries. In the central nervous system, HIV can induce a variety of abnormalities such as thinning of the corpus callosum and cortical atrophy (Thompson et al., 2005). Infection in a developing brain may lead to even more devastating defects such as white matter lesions, calcifications, and degeneration as a result of HIV encephalopathy or other indirect consequences of the virus (George et al., 2009). We scanned 120 children in Thailand using diffusion tensor imaging (DTI) to study white matter structural differences in infected versus uninfected children. We further assessed white matter associations with a Processing Speed Index (PS-I) while controlling for age, sex, and imaging site (**Table 1**). FDR ($q<0.05$) was used to control for false discoveries in the multiple regions tested. Using the ENIGMA-DTI processing protocol, we found white matter diffusivity was significantly associated with HIV status, in many brain regions including the *corona radiata* ($P= 0.002$; $Beta= 1.4x10^{-5}$) for mean diffusivity, and the corpus callosum ($P= 4.0x10^{-5}$; $Beta= 3.2x10^{-5}$) for axial diffusivity. Similar trends were seen when also controlling for treatment status. White matter associations were also detected with PS-I in the full group when also controlling for infection status. When assessed separately, we found in HIV-uninfected children, the radial diffusivity in many brain regions was significantly associated with PS-I, including the superior fronto-occipital fasciculus ($P= 0.003$; $Beta=-4.8x10^{-7}$). For HIV-infected children, however, after multiple comparisons correction only non-significant trend associations remained. These results provide evidence of structural and cognitive changes during development with HIV infection.

Table 1- Demographic factors for all HIV uninfected and infected children. Mean and standard deviation of data is presented; percentage is presented where appropriate. 88 of the 120 scanned children also completed cognitive evaluations used for this study.

Variables	HIV uninfected (55)	HIV infected (33)	*p-value*
Age *(mean +/- SD) in years*	10.7 +/- 2.6	11.7+/- 2.5	0.07
Sex *(% male)*	47%	33%	0.20
Imaging Site *(num)*			0.75
Chiang Mai University Hospital: Chiang Mai	28	18	
Chulalongkorn University Hospital: Bangkok	27	15	
School attendance *(% attended)*	100%	97%	
WISC-III Full Scale IQ *(mean +/- SD)*	82.9 +/- 14.0	73.6 +/- 9.9	**0.0012**
WISC-III Verbal IQ (V-IQ)	79.7 +/- 12.8	66.7 +/- 9.0	**<0.001**
WISC-III Performance IQ (P-IQ)	89.6 +/- 16.7	84.3 +/- 12.6	0.12
Verbal comprehension index (VC-I)	78.1 +/- 12.6	65.3 +/- 8.4	**<0.001**
Processing speed index (PS-I)	102.3 +/- 19.4	92.7 +/- 14.3	0.015
Freedom from distractibility (FD-I)	97.1 +/- 12.1	87.1 +/- 14.7	**<0.001**
Perceptual organization index (PO-I)	88.3 +/- 15.9	83.4 +/- 12.4	0.13

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Poster

570. Adolescent Development: Human Imaging

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Topic: A.09. Adolescent Development

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Title: Layer-specific comparison of high resolution MRI cortical thickness with the von Economo legacy

Authors: *L. H. SCHOLTENS, M. A. DE REUS, M. P. VAN DEN HEUVEL;
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Abstract: The human cortex harbors great spatial variety in cyto-, chemico- and myeloarchitecture. After detailed investigation of this rich variation in cortical cytoarchitectonics, pioneering anatomists von Economo and Koskinas published their monumental atlas (von Economo and Koskinas, 1925), reporting on a complete parcellation of the human cortex into 54 distinct cortical areas (and 107 detailed subregions) and quantitative data on cortical thickness and layer width (i.a.). Nowadays, Magnetic Resonance Imaging enables scientists to assess macroscale cortical thickness *in vivo*. Validating MRI cortical thickness measures by comparing von Economo whole-brain cytoarchitectural observations with MR-based cortical thickness estimates, we previously confirmed today's MRI technology as a good method for automated estimation of cortical thickness (Scholtens et al., in press). Extending these findings, we investigated the relation between regional von Economo individual cortical layer width and MR-based cortical thickness. The von Economo atlas includes a parcellation of the human cerebral cortex into 54 areas and regional cortical- and layer thickness data (von Economo and Koskinas, 1925). MR thickness estimates were derived from high-res MRI T1 data of 215+ subjects of the Human Connectome Project (Van Essen et al., 2013). Cross-technique analysis of cortical layer thickness was performed by correlation between mapped von Economo histological values and single hemisphere group-wise MR cortical thickness. MR-based total cortical thickness was associated with width of 5 out of 6 individual von Economo cortical layers (p=3.70x10-05, p=0.44 ns, p= 2.45x10-04, p=7.41x10-04, p=1.31x10-05, p=6.07x10-05, layer 1 to 6 resp.). Similar correlations were found within the von Economo data, where layer 3, 5 and 6 show a significant association with total cortical thickness, (p=2.84x10-14, p=8.11x10-13,

p=3.46x10-13). Examining the unique contribution of each layer to total MR thickness using multiple linear regression revealed the strongest unique contribution of layer 5 (β=0.742, p=0.0244), with layer 3 and 6 showing a trend-level effect, suggesting a unique contribution of these layers to the total cortical thickness, as derived by MR measurements. Comparing modern T1-weighted imaging to early histological findings of the von Economo atlas, we show von Economo individual cortical layer width to be associated with total cortical thickness as measured by MRI. Width of cortical layer 3, 5 and 6 shows the most consistent association, significantly contributing to total cortical width in both von Economo histological and MR-derived cortical thickness.

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Poster

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Support: NSF DGE-1247842

Title: Adolescent development of structural anterior cingulate cortex connectivity: meta-analysis of diffusion imaging studies

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Abstract: Objective: The anterior cingulate cortex (ACC) has been implicated in a broad array of higher-order cognitive, affective and behavioral functions by virtue of its distributed connectivity with multiple neural networks. Protracted maturation of white matter pathways that facilitate ACC connectivity, including the cingulum and anterior thalamic radiations (ATR), may impact the course of psychosocial development across adolescence and into young adulthood. The aim of the current meta-analysis was to draw from existing studies of white matter development to establish whether maturation of structural ACC connectivity is ongoing throughout adolescence and thus represents a viable mechanism for the integration of cognitive, affective, and social neural networks that continues into young adulthood. Methods: Studies reporting linear, quadratic, or logarithmic relationships between age and fractional anisotropy

(FA) of the cingulum and/or ATR were selected for inclusion in the meta-analysis (cingulum: N=10 studies, N= 2067 total participants; ATR: N=7 studies, N=1633 total participants). Regression models reported for each pathway were used to simulate FA for each age within the range included in each study. FA values were then converted to z-scores in order to standardize across studies, producing estimates of the predicted direction and magnitude of change in FA at each age for each pathway. Simulated data from each regression model and each study were combined and linear and quadratic effects of age on FA across the lifespan (age 0-90) and within adolescence (age 10-20) were compared. Results: Significant quadratic effects of age on FA were found for the cingulum (age beta = 1.597, p = .000; age^2 beta = -2.096, p = .000) and ATR (age beta = .903, p = .000; age^2 beta = -1.616, p = .000) across the lifespan. Looking specifically at the adolescent period, a significant linear effect of age on FA was observed in both the cingulum (beta = .218, p = .000) and the ATR (beta = .168, p = .000), but no quadratic effects were observed. Conclusions: These results suggest that structural ACC connectivity continues to strengthen throughout adolescence, and may contribute to changes in functional connectivity and improvements in cognitive, affective, and social functioning during this period.

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SBE-1041725

Title: Age of sign-speech bilingual language exposure and syntactic processing in deaf individuals with cochlear implants using functional near infrared spectroscopy (fnirs)

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Abstract: Studies of bilinguals are a powerful tool for exploring language experience-dependent brain changes throughout the lifespan. While the age of first bilingual exposure correlates with a greater extent and variability in classic LH language tissue (Kovelman, Baker, & Petitto, 2008),

questions remain about the neural impact of different bilingual language experiences, including dual modality deaf bilinguals who learn a visual language and a spoken language via a cochlear implant (CI). Theories have been advanced that early visual language experience negatively alters classic LH spoken language sites. Here, we ask if early sign-speech bilingual exposure alters neural sites and systems associated with spoken language syntactic processing, testing two hypotheses: (1) Early sign-speech bilingual exposure renders typical neural development supporting syntactic processing. (2) Only early spoken language experience results in normal neural development; early sign-speech bilingualism disrupts typical LIFG recruitment for syntactic processing. Methods. Deaf CI adults (mean implantation age 3 yr) with early (0-4 yr) or late (4+ yr) ASL exposure performing an English (SO-OS) sentence judgment task while undergoing fNIRS neuroimaging. Like fMRI, fNIRS measures hemodynamic response, but has key advantages for studying language: good spatial/temporal resolution (SR 10x/sec); tolerates movement; safe for CI individuals (Shalinsky et al., 2009). Results. Behavioral data revealed similar group performance on measures of reaction time and accuracy. CI individuals with either early or late ASL exposure showed typical LIFG recruitment when reading English sentences. By contrast, late bilinguals showed a greater extent and variability in activation of LH language areas and bilateral inferior parietal lobules. Early sign-speech bilingualism did not disrupt typical development of LIFG tissue recruited for syntactic processing, findings that shed new light on how the age of sign-speech bilingual language experience can impact the development of language processing in deaf CI individuals. Early sign-speech bilingual exposure showed no negative impact on English syntactic processing. Yet, later sign-speech bilingual exposure was correlated with a greater extent and variability in LH neural recruitment, showing a similar "neural signature" observed in studies comparing early and late-exposed bilinguals using two spoken languages (Jasinska & Petitto, 2013; Kovelman et al., 2008). Of broad significance, early bilingualism, regardless of modality (signed or spoken), supports healthy neural development mediating language processing in all individuals.

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Title: Exploring the anatomy and genetics of cortical asymmetries in surface area and thickness

Authors: *B. N. CIPOLLINI[1], H. BARTSCH[2], G. W. COTTRELL[1];
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Abstract: We use MRI and genetic assessments from the cross-sectional PING study (Jernigan et al., 2015) to quantify and inter-relate cortical asymmetries during development, with over 1000 subjects in the 3-20 year old age range. These data include surface-based parcellations via FreeSurfer, with estimates of surface area and thickness per cortical region of interest. Ongoing work examines asymmetries in subcortical volume and fiber tract measures, as well as association with behavioral and familial background. We found that asymmetries are extremely consistent across age, gender, and handedness. Left hemisphere (LH) structure correlations was more similar to correlations amongst structure asymmetries than right hemisphere (RH), suggesting when structures are asymmetric, they covary more consistently in the LH. Multivariate analyses (PCA) showed little evidence of strong covariations across asymmetries, whether tested within a measure (surface area) or across all of them. Instead, the data indicate separable asymmetries for frontal pole, cingulate cortex, entorhinal cortex, and inferior frontal gyrus / superior temporal sulcus. We ran 8 preliminary genetic association studies; four with the top cortical area asymmetries, one summary statistic of brain-wide asymmetry, and one for each of the top component of the three PCA analysis we ran. Despite our modest sample size (~1200 subjects), in two of the analyses we found a significant association between our strongest asymmetry, in the cortical area of the frontal pole, and SNP rs17281622 ($p<3E-8$). This SNP resides closest to the STK31 gene on chromosome 7; the two other most significant SNPs (rs10278268 and rs6957300) also reside near or within STK31. STK31 has been associated with spermiogenesis, however it is expressed in the brain and its role in spermiogenesis is likely duplicated by other TDRD-family genes, leaving its functional role an open question. We validated our approach by replicating findings on cortical asymmetries from smaller MRI-based studies in both development and adulthood. We show small changes in thickness asymmetries over development, but an overall lack of change in cortical area asymmetry across the age range studied. We qualitatively match effect sizes of surface area asymmetries throughout the brain reported in adulthood. We also replicate the finding that a summary statistic of asymmetry across the brain correlates positively with brain size.

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Title: Parcellating common neuroanatomical phenotypes across ASD, ADHD, and schizophrenia

Authors: *M. M. PARK[1,2], A. RAZNAHAN[3], P. SHAW[4], N. GOGTAY[3], J. P. LERCH[5], M. M. CHAKRAVARTY[2,6];
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Abstract: Background: Neuropsychiatric disorders such as autism (ASD), ADHD, and schizophrenia (SCZ) share common symptomatic dimensions and evidence of concomitant neuroanatomical vulnerabilities may underlie joint clinical phenotypes. Here, we examined neuroimaging biomarkers under the hypothesis that convergence of diagnostic effects in select brain regions may indicate: 1. Involvement of the region in mediating specific neurocognitive functions, which are further; 2. Coincident with the common underlying deficit across disorders. **Methods**: Brain scans from 34 sites (N=2307; 1300/453/233/321, controls/ASD/ADHD/SCZ) were processed using the CIVET pipeline for cortical thickness (CT) estimation and the MAGeT Brain algorithm for subcortical surface area (SA). Effects of diagnosis on CT and SA were examined using mixed-model regression analysis, accounting for age, sex, intracranial volume as fixed, and site as the random effect. Peak regions were re-assessed by random effects meta-analysis. **Results**: Within individual disorders, we found both similar and distinct patterns of grey matter alterations: diffuse increases in CT along the left hemisphere in ASD, ADHD showed largely reductions, and SCZ with significant brain-wide decreases (Fig a, b). Once analyzed in conjunction, findings converged along the orbitofrontal cortex (OFC), and ventral striatum (VS), with consistent direction of effects across disorders (Fig c). **Conclusions**: We found common grey matter reductions in regions known to mediate multiple cognitive deficits across disorders, i.e. abnormal reward and emotion processing and social cognition (OFC, VS). Results suggest mutual structural anomalies, signifying shared deficits in symptom dimensions. Further, these regions are richly interconnected and indicate additional disruption of fronto-striatal circuitry apart from individual changes. These findings provide novel insights into shared patterns of altered neurodevelopment and aging across a large multi-site cohort, and illustrate potential for mutual biomarkers across multiple disorders.

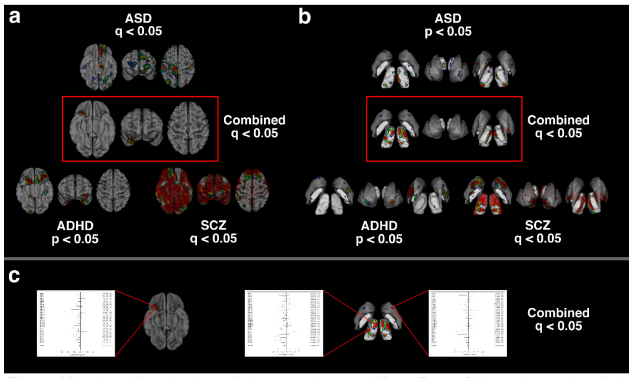

Figure. Mixed-model and meta-analysis regression, modelling effects of diagnosis on: a) cortical thickness and b) subcortical surface area. a, b) Within-disorder and combined mixed-model regression analysis. q < 0.05 indicates regions significant after FDR correction. Part of results in ASD and ADHD did not survive FDR correction. c) Meta-analysis within regions of peak significance for cortical thickness, thalamus, and striatum. Forest plots indicate magnitude and direction of disease-effects per site at the specified peak vertices.

Disclosures: **M.M. Park:** None. **A. Raznahan:** None. **P. Shaw:** None. **N. Gogtay:** None. **J.P. Lerch:** None. **M.M. Chakravarty:** None.

Poster

570. Adolescent Development: Human Imaging

Location: Hall A

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Program#/Poster#: 570.25/B17

Topic: A.09. Adolescent Development

Support: ([FP7/2007-2013] [FP7/2007-2011]) number 602621

Title: Individual structure-function relations within the default-mode network as a result of normal aging

Authors: ***M. AVRAM**[1], L. PASQUINI[2], J. BÄUML[2], V. RIEDL[3], C. SORG[4];
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Abstract: Structure-function relationships, a pervasive topic in biology, are beginning to be well understood at the cellular level - for instance, different neuron types and their structural connections are intimately coupled with their function and correspondent activity (Honey et al., 2010). However, this correspondence remains unclear in neural systems, particularly at the level of macroscopic networks. In the present study we investigated whether structure-function

correspondence can be found in macroscopic networks in the individual brain, specifically in the default-mode network (DMN), and whether this correspondence is modulated by normal ageing. Resting state functional MRI data and structural MRI data was sampled for 23 young healthy subjects (mean age 26, 8 females) and 20 elderly healthy subjects (mean age 67, 13 females). We focused on two different measures, and their correspondence: (1) coherence of intrinsic activity - represented by functional connectivity (iFC) of ongoing blood oxygenation level dependent (BOLD) activity in selected intrinsic brain networks, and (2) brain structure - represented by cortical thickness. Independent component analysis was used to derive 25 components from iFC, reflecting a set of intrinsic brain networks and physiological noise. The component matching DMN was selected, and mapped via dual regression onto each subject's 4D dataset. Finally, individual DMN z-maps where projected into individual vertex-space. The output measure, structure-function correspondence (SFC), was determined by calculating the individual correlation coefficient (Spearman) of CT and iFC values within DMN. Results indicate positive SFC both at the individual and group level. In a second step, group differences were tested via an ANCOVA model using the number of vertices as a covariate of no interest. There was a significant effect of group (young > old) on SFC within DMN, $F(1, 161) = 6{,}86$, $p = .01$. The number of vertices had no effect on SFC, $p = .48$. We provide evidence that: (1) There is a positive relationship between iFC and CT in DMN in the individual brain, (2) SFC seems to be age dependent considering its decrease with normal ageing. These results are in line with previous work regarding the effects of ageing on the DMN measured either by iFC or CT (Damoiseaux et al., 2008; Kalpouzos et al., 2012). Thus, SFC could provide a valuable measure that may illustrate individual structure-function dynamics, and putative modulatory effects of biological processes such as ageing and pathology.

Disclosures: **M. Avram:** None. **L. Pasquini:** None. **J. Bäuml:** None. **V. Riedl:** None. **C. Sorg:** None.

Poster

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Topic: A.09. Adolescent Development

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Veterans Affairs grant IK2CX000772

Title: Neurodevelopmental sex differences in response to emotional faces

Authors: J. C. SCOTT[1], K. RUPAREL[3], D. H. WOLF[2], T. SATTERTHWAITE[2], R. HOPSON[2], M. QUARMLEY[2], P. VILLA[2], R. E. GUR[2], *R. C. GUR[2];
[1]Psychiatry, [2]Univ. Pennsylvania, Philadelphia, PA; [3]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Background: Knowledge regarding developmental sex differences in affective processing across a broad age range is still limited, as most studies have had small samples or have focused on a narrow age range. Here, we aimed to examine developmental sex differences in affective processing in a large sample of children, adolescents, and young adults. Methods: From the Philadelphia Neurodevelopmental Cohort, 307 typically developing youths age 8-21 with no significant psychopathology underwent fMRI while performing a well-validated task of emotion identification. Sixty faces displaying neutral, happy, sad, angry, or fearful expressions were presented, and participants were asked to label the emotion presented. fMRI subject-level statistical analyses were conducted in FSL with motion correction parameters included as nuisance covariates. Voxelwise whole-brain analyses employed linear mixed-effects analysis (FLAME1). Task contrast maps were entered into second level analyses adjusted for task accuracy, participant race, and motion and with cluster correction for multiple voxelwise comparisons, and linear and nonlinear trends were tested. Results: Significant age by sex interactions in BOLD response were present in ventromedial and dorsolateral prefrontal cortex and the cuneus to all emotions versus baseline ($p<.05$). Follow-up analyses indicated that females evidenced linear increases in activation with increasing age in these regions, while males evidenced only slight decreases over time with increasing age. Conclusions: In a large sample of typically developing youth, we found developmental sex differences in response to emotional faces in ventromedial and dorsolateral prefrontal regions, such that females showed progressive increases in activation with age while males showed minimal age-related effects in these regions. These findings suggest maturational sex differences in circuitry responsible for the cognitive regulation of emotion. Notably, however, no significant age by sex interactions were found in the amygdala or other limbic circuitry. Nonetheless, longitudinal research is needed to more thoroughly probe developmental trajectories of brain response to affective processing.

Disclosures: J.C. Scott: None. **K. Ruparel:** None. **D.H. Wolf:** None. **T. Satterthwaite:** None. **R. Hopson:** None. **M. Quarmley:** None. **P. Villa:** None. **R.E. Gur:** None. **R.C. Gur:** None.

Poster

570. Adolescent Development: Human Imaging

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Topic: A.09. Adolescent Development

Support: RO1 MH069942

Stony Brook Research Foundation

Title: The influence of higher order regions on developing visual category specialization in children

Authors: *J. F. O'RAWE, A. HUANG, D. KLEIN, H.-C. LEUNG;
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Abstract: Visual association areas along the ventral visual pathway exhibit selective activity in correspondence to different types of stimuli. This selectivity, however, seems to develop throughout childhood. Several neuroimaging studies have shown that face specific processing in the fusiform gyrus seems to emerge between the ages 8-15. Within this same time frame, brain regions which receive and send feedback projections to these visual association areas, such as the amygdala and posterior parietal cortex, are undergoing major developmental changes. To examine whether the development of these higher order regions influences the development of category specialization in visual association cortices, we collected both task and resting state fMRI data from a sample of 40 children (16 female) ages 9-12 (M = 10.4, SD = 0.93) using a 3T Siemens Trio System. The identity matching task was in a block design with 3 face conditions (happy, sad, and neutral faces) and a house condition as the control condition. The task blocks were intermixed in pseudorandom orders and separated by fixation blocks. Each participant performed one run, containing 3 blocks of each condition (12 total blocks; 6.2 minutes). In the resting state scan, we collected 11.7 minutes of fMRI data during which participants were instructed to fixate at a target of concentric circles. Univariate analysis of the task data revealed greater activity in response to faces than to houses in the typical nodes of the face processing network, including the fusiform gyrus, superior temporal sulcus, anterior temporal face patch, and the amygdala. The opposite comparison revealed activity in the typical nodes of the scene processing network, including the parahippocampal gyrus, retrosplenial cortex, transverse occipital sulcus, and posterior parietal areas. As shown in previous studies, we observed weaker activity in the face processing network compared to what has been observed for adults. Utilizing the resting state scans, we characterized the connectivity patterns of the amygdala and the superior parietal lobe, revealing substantial overlap in both the parahippocampal and fusiform gyri. Utilizing this region of overlap in the fusiform gyrus, we found that the variance in fMRI signal during the face blocks of our task could partly be explained by the interaction between activity in the amygdala and activity in the superior parietal lobe. Our results suggest that one possible contribution to the emergence of the specialization of visual association regions is the

recruitment of higher order brain regions that send feedback projections, presumably modulating activity in these regions.

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Poster

570. Adolescent Development: Human Imaging

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Program#/Poster#: 570.28/B20

Topic: A.09. Adolescent Development

Support: MH067924

Title: Reliability in engagement of maintenance and retrieval brain activation states underlies longitudinal improvements in working memory

Authors: ***D. F. MONTEZ**[1], D. SIMMONDS[1], B. LUNA[2];
[1]Neurosci., [2]Psychiatry, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Working memory (WM) improves through adolescence largely due to age related decreases in the variability of responses. The neural basis for improvements in the reliability of WM performance is not well understood. The present study aimed to characterize trial-to-trial behavioral variability that can be attributed to variability occurring within purely motor or purely cognitive processes and to characterize the relative changes in their contribution to behavioral variability at different ages. We examined a mixed longitudinal cohort of subjects, between the ages of 8 and 30, as they performed a variant of the memory-guided saccade task during fMRI acquisition. We identified a set of canonical BOLD signal brain states, or whole-brain patterns of activity, that are associated with eye-movement motor responses, working memory maintenance, and memory-guided eye movements. We applied dimensionality reduction techniques to assess subject-level trial-to-trial variability of recruitment of networks supporting WM maintenance and retrieval as well as oculomotor performance. The results of our analyses demonstrate that performance of a spatial WM task relies on measurable independent contributions from motor and cognitive brain states. Variability in performance on individual trials is the result of differences in the degree to which motor and cognitive brain states are expressed on individual trials. We provide evidence that the magnitude of brain state variability in oculomotor systems is approximately fixed by late childhood but cognitive brain state variability _that variability associated with the maintenance and retrieval of spatial information_ continues to decrease during the same time. We therefore conclude that the primary driver of reduced behavioral

variability during adolescent development is the continued refinement of cognitive- and not occulomotor- related brain systems.

Disclosures: D.F. Montez: None. **D. Simmonds:** None. **B. Luna:** None.

Poster

570. Adolescent Development: Human Imaging

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Topic: A.09. Adolescent Development

Support: MacArthur Foundation Research Network on Law and Neuroscience

Title: Network modularity increases as the "social brain" matures: a gray matter covariance approach

Authors: *K. FETTICH[1], A. O. COHEN[2], K. S. BREINER[3], D. DELLARCO[2], A. GALVAN[3], B. J. CASEY[2], L. STEINBERG[1], J. M. CHEIN[1];
[1]Temple Univ., Philadelphia, PA; [2]Sackler Inst. for Developmental Psychobiology, Weill Med. Col. of Cornell Univ., New York, NY; [3]UCLA, Los Angeles, CA

Abstract: Adolescence is a sensitive period for social information processing, which is thought to rely on the functional and structural maturation of "the social brain" network (Blakemore, 2008). The maturation of this network, however, is not yet fully understood. The present study used gray matter covariance to characterize the modular architecture of the social brain network as it changes across development, from adolescence and adulthood, and investigated the hypothesis that the social brain network becomes more specialized (Bickart et al., 2014), and hence more modular with maturation. Subjects were 76 adolescents and 60 adults recruited through the MacArthur Foundation Research Network on Law and Neuroscience. Gray matter volumes were obtained for 15 structures bilaterally and entered into a symmetric covariance matrix that was binarized and FDR-thresholded (q=.01). The resulting matrix was then used to compute modularity, with significance testing implemented via Monte Carlo simulations with participant subsamples from each age group. For each subsample, an average cortical thickness score was also computed as an index of cortical maturation. Results indicate an inverse relationship between the structural modularity of the social brain network and global cortical thickness, r=-.412, p<.001. Networks derived from the adolescent subsamples had significantly thicker cortex means (M= 2.59, SD=.01; t(78) = 45.08, p<.001) and lower modularity (M=.66, SD=.18;t(57.38)=-3.71, p<.001) than did the networks derived from the adult subsamples

(thickness: M=2.49, SD=.01; modularity: M=.77, SD=.09). These findings suggest that, within the brain regions known to process social information, the relationships between regional volumes change with maturation, resulting in a more modular adult social brain architecture. Covariation in gray matter volume may result from functional specialization, and analyses of gray matter covariance could help advance our understanding of morphological maturation from a regional focus to a broader systems-level perspective.

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Poster

570. Adolescent Development: Human Imaging

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Topic: A.09. Adolescent Development

Support: ERC-2012-StG-313481

Title: Effects of aging on T1, T2*, and QSM values in the subcortex using 7T MRI

Authors: *M. C. KEUKEN[1], A. SCHAFER[2], K. BACKHOUSE[1], S. BEEKHUIZEN[1], L. HIMMER[1], A. KANDOLA[1], J. LAFEBER[1], L. PROCHAZKOVA[1], A. TRUTTI[1], R. TURNER[2,1], B. FORSTMANN[1], P.-L. BAZIN[2];
[1]UvA, Amsterdam, Netherlands; [2]Max Planck Inst. for Human Cognitive and Brain Sci., Leipzig, Germany

Abstract: Ultra-high field 7T MRI has made significant contributions over the last years in understanding the relationship between structure and function of the human brain. It allows the visualization of small subcortical structures with different tissue properties with tailored MRI sequences. However, the impact of structural changes associated with healthy aging on the visibility of such small subcortical structures remains largely unknown. In the present study, ultra-high field 7T MRI was used to segment the striatum, globus pallidus internal and external, subthalamic nucleus, substantia nigra, red nucleus, periaqueductal grey, as well as the lateral ventricles, 3th ventricle, aqueduct, and 4th ventricle in young (n: 30, mean age: 23.8, SD: 2.3), middle aged (n: 14, mean age: 52.5, SD: 6.6), and elderly healthy participants (n: 10, mean age: 69.6, SD: 4.6). The individual masks were used to extract the volume of the structure and the T_1, T_2^*, and quantitative susceptibility map (QSM) values. The volumetric measures generally showed a significant decrease with age in grey matter volume and an increase in ventricle

volume. The T1 values generally increased with age, likely reflecting a decrease in myelination, whereas the T2* and QSM values showed a more variable pattern reflecting the effect of increased iron deposition. In sum, the results of the present study indicate that structural changes in the subcortex associated with healthy aging influence the T_1, T_2^*, and QSM values differently, which may have an impact on structural delineations and volumetry. To characterise each subcortical structure better, it may be helpful to integrate multiple MR contrasts.

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Poster

571. Amino Acids

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 571.01/B23

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: HCDP -KRG -IRAQ

Title: How the inhibitory modulator GABA alters development, behavior and neuronal circuit function in *Drosophila*

Authors: *D. D MAHMOOD[1,2], N. DABBAIN[1], J. GRAFF[3], Z. MAJEED[1,4], R. L. COOPER[1]; [1]Biol., Univ. of Kentucky, Lexington, KY; [2]Biol., Univ. of Sulaimani, Sulaimani, Iraq; [3]Emory Univ., Atlanta, GA; [4]Biol., Univ. of Salahaddin, Erbil, Iraq

Abstract: *Drosophila* melanogaster is a simple model system that provides an advantage over vertebrates because of their less complex nervous system and the ability to make modifications genetically for studies on identifiable cells. Key questions in understanding the function of the central nervous system (CNS) in physiologic and pathologic conditions can be addressed in this system quickly and cheaply to develop a foundation which can be followed up in mammalian systems. Neuromodulators and neurotransmitters play a significant role in the activity of the CNS. Many studies address the effects of enhanced activity on synapse formation and axon growth but few address the effects of reducing activity or the effects of GABA, an inhibitor modulator in the brain. Our central research question is on the role of GABA, on the development and maintance of neural circuits and in relation to animal behavior. We examined the effects of administering varying levels of GABA to the organisms through tests on development, behaviors, olfaction, survival and physiology. The developmental time to pupation

and to eclosion as well as behavioral tests were also investigated. The larval development has been shown to be slowed in a dose-dependant manner with feeding GABA. Locomotive behavior was not altered, but mouth hook movements were reduced in the third instar larvae that were fed GABA. This study shows that GABA retarded larval development and altered behavior. We are now addressing GABA directly on the larval CNS and assessing neural activity as well as direct actions on the larval heart. Directly applying GABA onto exposed 3rd instar hearts unexpectedly increases the heart rate. This study has implications regarding dietary supplements and pharmacological agents used clinically that modify the GABAergic system in the CNS of humans. This multifaceted project is attempting to understand the effects of GABA on several levels from the exogenous aspects, to the altering of neuronal activity for the treatment of diseases. This study may help to address concerns of GABA being sold in common dietary supplements.

Disclosures: D. D Mahmood: None. **N. Dabbain:** None. **J. Graff:** None. **Z. Majeed:** None. **R.L. Cooper:** None.

Poster

571. Amino Acids

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Program#/Poster#: 571.02/B24

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIMH R01MH096946

NARSAD young investigator grant

Title: Quantitative brain-wide mapping of GABAergic neuronal subtypes in mice

Authors: *Y. KIM[1], K. UMADEVI VENKATARAJU[1], K. PRADHAN[1], G. FITZGERALD[1], M. HE[2], J. LEVINE[1], Z. HUANG[1], P. OSTEN[1];
[1]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Inst. of brain science, Fudan university, Shanghai, China

Abstract: Recent advances in mouse genetic tools enable the identification and labeling of different neuronal subtypes, and promises to help in unraveling the cellular complexity of the mammalian brain. However, a lack of tools for quantitative brain-wide mapping of the genetically identified cell types has been a major constraint towards quantitative assessment of their distribution. Here, we use serial two-photon (STP) tomography and a data processing

pipeline, termed “qBrain” for quantitative brain-wide mapping, to provide the first whole brain quantification of three major cortical interneurons expressing parvalbumin (PV), somatostatin (SST) and vasoactive intestinal peptide (VIP). Our analysis reveals the numbers and densities of the three neuronal populations per anatomical regions of the Allen Mouse Brain Atlas and 3D sphere voxels. The three populations show distinct spatial patterns in cortical and subcortical regions. Furthermore, brain-wide statistical comparison between male and female brains revealed sexually dimorphic brain areas in SST neurons. In contrast to the relatively homogenous PV neurons, SST and VIP populations each contains subtypes. Thus, we used genetic intersectional approach to further distinguish SST subtypes co-expressing either calretinin (CR) or nitric oxide synthase (nNOS), and VIP subtypes co-expressing either CR or cholecystokinin (CCK). In the isocortex, both VIP/CCK and VIP/CR neurons are expressed mainly in the superficial layer. In SST intersection, SST/CR and SST/nNOS neurons are highly expressed in superficial and deep cortical layers, respectively. Our dataset provides a comprehensive resource for cell type-based manipulation experiments and *in silico* neuronal network modeling.

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Poster

571. Amino Acids

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Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grant R15GM110690

Title: SLC1A4 and SLC1A5 mediate transport of D-serine in brain

Authors: J. C. FARNSWORTH[1], G. E. LIND[1], B. R. LYDA[1], N. R. NATALE[2], *M. P. KAVANAUGH[3];
[1]Neurosci., [2]BMED Neurosci., [3]Univ. of Montana, Missoula, MT

Abstract: SLC1A4 and SLC1A5 constitute a subfamily of sodium-dependent amino acid exchangers within the SLC1 gene family that also contains the glutamate transporter subfamily. SLC1A4/A5 (ASCT1/2) are expressed in the CNS and they mediate transmembrane flux of many neutral amino acids including the eponymous substrates L-Ala, L-Ser, and L-Cys. SLC1A5/ASCT2 additionally displays selectivity for L-Gln. The functional roles of SLC1A4/A5 transporters in the brain remain largely unknown. D-serine is an endogenous co-agonist at

synaptic NMDA receptors and it plays critical roles in signaling and synaptic plasticity. The heteromeric sodium-independent amino acid transporter asc-1 (SLC7A10/SLC3A2) has been shown to mediate uptake of D-Ser, but many details of the homeostatic mechanisms controlling D-Ser levels in the CNS are not fully understood. As both L- and D-aspartate are recognized by homologous SLC1 glutamate transporter subfamily members, we examined D-Ser transport in Xenopus laevis oocytes expressing SLC1A4 and SLC1A5 and found that contrary to some reports in the literature, [3H] D-Ser was taken up by each and induced anion currents with Km values of 121 μM and 65 μM, respectively. We synthesized and characterized a novel molecule, (2S,3R,4R)-4-(biphenyl-4-ylmethoxy)-3-hydroxy-pyrrolidine-2-carboxylic acid (BOCA), that inhibited both SLC1A4/A5 transporters at nanomolar concentrations. Approximately one-half of [3H] D-Ser uptake in acute adult mouse brain slice was found to be Na-dependent and sensitive to block by BOCA, suggesting a critical role for SLC1A4/A5 transporters in the modulation of D-Ser levels in the brain. These results expand the repertoire of transport mechanisms in the brain for D-Ser. Importantly, as NMDAR dysfunction has been implicated in a number of neurodegenerative and psychiatric disorders, these transporters may become a critical therapeutic target, and blockers such as BOCA and its analogs could play a role in the treating these disorders.

Disclosures: **J.C. Farnsworth:** None. **G.E. Lind:** None. **B.R. Lyda:** None. **N.R. Natale:** None. **M.P. Kavanaugh:** None.

Poster

571. Amino Acids

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Support: NIH-K01DA026504

NIH-R01DA036612

NIDA-INSERM fellowship (VZ)

TRDRP-22FT-0063 (JHY)

Title: Role of ventral tegmental area glutamate neurons in behavioral reinforcement

Authors: *J.-H. YOO, V. ZELL, J. WU, A. JOHNSON, R. RESSLER, M. A. SHENASA, C. A. PUNTA, K. H. FIFE, N. A. GUTIERREZ-REED, T. S. HNASKO;
Neurosciences, UCSD, La Jolla, CA

Abstract: The ventral tegmental area (VTA) plays an important role in both positive and negative behavioral reinforcement. Recent physiological and neuroanatomical studies suggest that VTA glutamate neurons make functional synapses onto lateral habenula, ventral pallidum, nucleus accumbens and other limbic regions where they can co-release other transmitters, namely dopamine or GABA. Here we expand upon earlier physiological and anatomical studies and investigate whether selective optogenetic activation of VTA glutamate neurons promote behavioral reinforcement or avoidance. We find that photostimulation of VTA glutamate somata or terminals can lead to opposing and projection-target dependent effects on behavioral reinforcement. These results suggest that VTA glutamate neurons serve a unique and state-dependent roles in driving goal-directed behaviors

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Poster

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Wallin Discovery Fund

Inserm

CNRS

Université Claude Bernard Lyon I

Title: Enzymatic biosensor measurements of dynamic, light-evoked release of the NMDA receptor coagonist D-serine in the retina

Authors: *E. C. GUSTAFSON[1], S. MARINESCO[2], R. F. MILLER[1];
[1]Neurosci., Univ. Minnesota, Minneapolis, MN; [2]Ctr. de Recherche en Neurosciences de Lyon, Univ. Lyon 1, Lyon, France

Abstract: D-serine is an essential co-agonist for activation of retinal ganglion cell NMDA receptors. The mechanisms that regulate D-serine availability to these receptors are poorly understood. To investigate these processes, we have utilized a biosensor that detects D-serine to nM levels. Biosensors were constructed by inserting a 25 μm diameter 90% Pt/ 10% Ir wire into a pulled glass capillary. A layer of m-phenylenediamine was place on the wire protruding from the glass to block non-specific oxidation. Then an enzymatic layer containing D-amino acid oxidase (DAAO) in a BSA solution was applied to the tip for D-serine sensitivity. Control electrodes were made by excluding DAAO from the final layer. We used a micromanipulator to manipulate the biosensors onto the surface of the retina in a mouse retina-eyecup preparation. Changes in electrode current, measured with a VA-10 amplifier (NPI Electronics), were monitored in response to light stimuli projected onto the retina as well as to responses during bath application of pharmaceutical agents. Biosensor currents showed a linear relationship with D-serine standards from 100 nM to 100 μM. A resting, background level of D-serine was determined by applying the D-serine degrading enzyme D-serine deaminase (DsdA). Following light simulation, a dynamic release of D-serine was measured. Application of pharmaceutical agents indicated that multiple mechanisms were involved in light-evoked D-serine release in the retina, including activation of glutamate receptors.

Disclosures: E.C. Gustafson: None. **S. Marinesco:** None. **R.F. Miller:** None.

Poster

571. Amino Acids

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 571.06/B28

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grant R01DA036612

NIH Grant K01DA026504

Title: Afferent inputs of transmitter-defined neuronal populations of the ventral tegmental area

Authors: *L. FAGET[1], J. DUAN[1], R. RESSLER[1], F. OSAKADA[2], E. M. CALLAWAY[2], T. S. HNASKO[1];

[1]Neurosci. Dept., UCSD, LA Jolla, CA; [2]Systems Neurobio. Labs., Salk Inst. for Biol. Studies, La Jolla, CA

Abstract: The ventral tegmental area (VTA) has achieved a central status in the neural circuit control of behavioral reinforcement. Though generally considered a dopaminergic nucleus, the VTA contains substantial heterogeneity in neuron type, including both GABAergic and glutamatergic neurons. Understanding anatomical connectivity is essential to understanding how neural circuits control behavior. However little is known regarding how VTA neuron types, particularly VTA glutamate neurons, may be differentially regulated by distinct afferent inputs. We used a recently developed combinatorial viral approach using Glycoprotein-deleted Rabies virus (RVΔG) to transynaptically label afferent inputs to genetically identified dopamine, GABA, or glutamate neurons of the VTA. This approach enabled specific rabies virus replication and transynaptic transport in each of the VTA neuronal populations and the characterization of cell type-specific afferent inputs. We observed that nucleus accumbens, ventral pallidum, lateral habenula, hypothalamus, raphe nuclei, cortical and tegmental regions among others all send projections to each of the 3 transmitter-defined VTA cell types. Though afferent input is qualitatively similar, there appear to be quantitative differences suggesting specific inputs differentially target specific VTA cell types. Overall, these data shed important light on the organization of diverse inputs to VTA and to our understanding of the essential systems-level circuit structure of this important center in addictive behavior.

Disclosures: L. Faget: None. **J. Duan:** None. **R. Ressler:** None. **F. Osakada:** None. **E.M. Callaway:** None. **T.S. Hnasko:** None.

Poster

571. Amino Acids

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 571.07/B29

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH MH082881

Title: A neurotensin-producing cell population of the subiculum forms glutamatergic synapses with both principal neurons of the entorhinal cortex and dentate gyrus

Authors: *N. I. CILZ, S. LEI;
Pharmacology, Physiology, & Therapeut., Univ. of North Dakota, Grand Forks, ND

Abstract: The perforant pathway is largely comprised of axons emanating from layer II stellate neurons of the entorhinal cortex (EC) that synapse on to granule cells of the dentate gyrus (DG). Previously, our lab has shown that exogenous application of neurotensin (NT) increases the excitability of layer II neurons in the EC and granule cells of the DG. These observations raise the question as to where endogenous NT may originate in order to influence this pathway. In an effort to address this question, we utilized a cre-lox genetic approach to selectively express channelrhodopsin-EYFP in NT-producing cell types. Consistent with previous NT expression studies, we found that EYFP expression is confined largely to the subiculum. Photostimulation of the local recording region elicits excitatory postsynaptic currents (EPSCs) in both EC and DG principal neurons. These EPSC's are completely blocked in the presence of tetrodotoxin (0.5 μM), confirming that photocurrents are generated in presynaptic neurons. Application of the AMPA receptor antagonist DNQX (10 μM) and NMDA receptor antagonist APV (50 μM) completely abolishes the EPSCs, indicating NT-producing neurons are glutamatergic. Prolonged stimulation hyperpolarizes postsynaptic EC neurons. These results offer preliminary functional insight into NT-producing neurons of the subiculum and this model will be used to further probe for endogenous actions of NT.

Disclosures: **N.I. Cilz:** None. **S. Lei:** None.

Poster

571. Amino Acids

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 571.08/B30

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: Deutsche Forschungsgemeinschaft

Carlsberg Foundation

Title: The enzyme glutamate dehydrogenase is important for glutamate entrance in the tricarboxylic acid cycle in isolated nerve terminals

Authors: *M. C. HOHNHOLT, H. S. WAAGEPETERSEN;
Univ. of Copenhagen, Kobenhavn O, Denmark

Abstract: The enzyme glutamate dehydrogenase (GDH) catalyses the oxidative deamination of glutamate to alpha-ketoglutarate or the reverse reaction. This reaction connects major cellular pathways such as the tricarboxylic acid cycle and amino acid metabolism. Moreover, glutamate

is the most abundant excitatory amino acid in the brain and GDH might thus be important in neurotransmitter metabolism. To investigate the role of GDH in neuronal metabolism, nerve terminal endings (synaptosomes) were isolated from mice with a central nervous system specific deletion of glutamate dehydrogenase 1 (GDH1-deficient synaptosomes) or from control mice (control synaptosomes). The synaptosomes were incubated with 0.25 mM [U-13C]glutamate for 45 minutes and the occurrence of 13C-labelled metabolites was investigated by gas chromatography mass spectrometry. GDH1-deficient synaptosomes had a slightly higher cellular percent labelling of [U-13C]glutamate compared to control synaptosomes. But the first metabolite in the tricarboxylic acid (TCA) cycle generated directly from [U-13C]glutamate, [U-13C]alpha-ketoglutarate was significantly less labelled in GDH1-deficient synaptosomes compared to control. Other TCA cycle intermediates generated from [U-13C]glutamate, such as [U-13C]succinate, [U-13C]fumarate and [U-13C]malate were also less labelled in GDH1-deficient synaptosomes. In contrast, almost no differences in labelling in the isotopomers generated in the first turn of the TCA cycle, i.e. triple labelled alpha-ketoglutarate and double labelled succinate, fumarate and malate, were observed in GDH1-deficient synaptosomes compared to control synaptosomes. These data suggest that GDH plays an important role for the entrance of glutamate into the TCA cycle, but might not determine the subsequent cycling of glutamate-derived carbon in the TCA cycle.

Disclosures: M.C. Hohnholt: None. **H.S. Waagepetersen:** None.

Poster

571. Amino Acids

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 571.09/B31

Topic: B.01. Neurotransmitters and Signaling Molecules

Title: Actions of 3-hydroxykynurenine (3-HK), a tryptophan metabolite, on synaptic transmission in the mouse hippocampus and thalamus

Authors: *R. T. NGOMBA[1,2], S. A. NEALE[2,3], S. L. S. DUNN[2], R. SCHWARCZ[4], T. E. SALT[2];
[1]IRCCS Neuromed, Pozzilli 86077, Italy; [2]Visual Neurosci., UCL Inst. of Ophthalmology, London, United Kingdom; [3]Neurexpert Ltd, London, United Kingdom; [4]Maryland Psychiatric Res. Ctr., Dept. of Psychiatry, Univ. Maryland Sch. Med., Baltimore, MD

Abstract: The kynurenine pathway is a major route of tryptophan metabolism, and this pathway may be disturbed in several psychiatric and neurodegenerative disorders (Schwarcz *et al* 2012).

3-hydroxykynurenine (3-HK), a metabolite arising from tryptophan, is a precursor for several kynurenines, including xanthurenic acid (XA). We have previously shown that XA can reduce synaptic transmission in various brain areas, and that this may be related to inhibition of vesicular glutamate transport (VGluT) (Neale *et al* 2013, 2014). In order to investigate these pathways further, we studied the actions of 3-HK on synaptic transmission in the hippocampal dentate gyrus (DG) and the ventrobasal thalamus (VB), two brain areas that are involved in cognitive processes and psychiatric conditions. Either parasagittal (for DG) or horizontal (for VB) *in vitro* slice preparations were made from the brains of adult C57BL/6 mice. Recordings were made in an interface bath at ~33C. In the DG, stimulation of the perforant path with pairs of pulses (40 ms interval) resulted in excitatory post-synaptic field potentials (fEPSPs) that showed paired-pulse depression. Application of 3-HK (0.1-1 mM) resulted in a concentration-dependent depression of fEPSP amplitude (1 mM; 42 ± 11% depression), which reversed on washout. The paired-pulse ratio was unchanged by 3-HK. In comparison, we have shown that 10 mM XA was necessary to produce a comparable reduction of transmission in the DG (Neale *et al* 2013). In thalamic slices, extracellular multiunit spike recordings following stimulation of the internal capsule were made, revealing 86±3% of spikes occurring in bursts. Application of 1 mM 3-HK caused a reversible increase in the number of spikes recorded by 56±24%, however the proportion of spikes occurring in bursts did not change. Similarly, 1 mM XA caused a reversible increase in spikes by 53±40% with no change in the proportion of spikes in bursts. In summary, we have shown that 3-HK, the direct precursor of XA, has similar effects to XA in both hippocampus and thalamus. This finding is consistent with the idea that changes in 3-HK levels, either alone or by driving XA formation, produce effects on neuronal circuit function. This may be important in our understanding of how malfunction of tryptophan metabolism can cause neuropathological changes. Neale, SA *et al* (2013) Neuropsychopharmacol 38: 1060-1067. Neale, SA *et al* (2014) Neurochem International 73: 159-165. Schwarcz, R *et al* (2012) Nat Rev Neurosci 13: 465-477.

Disclosures: **R.T. Ngomba:** None. **S.A. Neale:** None. **S.L.S. Dunn:** None. **R. Schwarcz:** None. **T.E. Salt:** Other; Director of Neurexpert Ltd.

Poster

571. Amino Acids

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 571.10/B32

Topic: B.01. Neurotransmitters and Signaling Molecules

Title: High-throughput detection of Glycine in biological samples based on a novel enzymatic assay

Authors: G. E. CHAVARRIA, ***K. C. SCHMITT**, N. TIBREWAL, S. SADDAR, P. SAINI, G. TCHAGA, G. YAN;
Biovision, Milpitas, CA

Abstract: Glycine is the simplest of the twenty standard amino acids commonly found in proteins. Glycine functions as an important fast inhibitory neurotransmitter in the CNS, particularly in the spinal cord and brainstem. For example, spinal ionotropic glycine receptors regulate neuromotor function and skeletal muscle activity. Glycine also affects synaptic plasticity by acting as a co-agonist at NMDA receptors. Supplementation with exogenous glycine has been used in patients suffering from anemia, hypoglycemia, chronic fatigue, insomnia, obsessive compulsive disorder, epilepsy, memory disorders, and schizophrenia. Therefore, accurate and cost-effective detection methods are needed to validate the roles of glycine in neurological disorders. Traditionally, the concentration of glycine and other amino acids in clinical and non-clinical settings is determined by ELISA, NMR, HPLC, and Mass Spectrometry techniques, but these methods require expensive instruments and complex protocols that need to be performed by trained personnel. Enzymatic assays using one or more enzymes are routinely used for the detection of specific metabolites. Coupled-enzymatic assays are often preferred over complicated techniques due to the high specificity that enzymes show for their substrates, thus reducing potential interference. Additional advantages of enzymatic assays include superior reproducibility, high-throughput adaptability, and minimal sample requirement. BioVision, Inc. has developed the first Glycine Assay Kit using a coupled-enzymatic assay to detect this amino acid. The principle of the assay is based on the oxidation of glycine producing an intermediate that reacts with a fluorophore, producing a stable signal which is stoichiometrically proportional to the amount of glycine in the sample. The assay is glycine-specific and other standard and non-standard amino acids do not interfere with the assay. The assay is able to detect physiological concentration of glycine in a variety of biological samples utilizing 96-well plate and a microplate reader. Sample preparation is minimal and does not require laborious steps. In conclusion, BioVision's Glycine Assay Kit provides a unique, simple, sensitive, cost effective, and high-throughput assay for the detection of this amino acid.

Disclosures: G.E. Chavarria: A. Employment/Salary (full or part-time):; Full Time. **K.C. Schmitt:** A. Employment/Salary (full or part-time):; Full Time. **N. Tibrewal:** A. Employment/Salary (full or part-time):; Full Time. **S. Saddar:** A. Employment/Salary (full or part-time):; Full Time. **P. Saini:** A. Employment/Salary (full or part-time):; Full Time. **G. Tchaga:** A. Employment/Salary (full or part-time):; Full Time. **G. Yan:** Other; Owner.

Poster

571. Amino Acids

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 571.11/B33

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grant AG012993

NIH Grant AG035982

Title: Molecular mechanisms of neuroprotection against hypoxia in a hyperglutamatergic state and the role of mitochondrial K+ channels and HIF1a

Authors: *E. K. MICHAELIS, D. HUI, R. PAL, M. L. MICHAELIS, X. WANG;
Dept Pharmacol & Toxicol, Univ. Kansas, Lawrence, KS

Abstract: Most investigations into the effects of glutamate (Glu) on neuronal survival have been focused on Glu-induced neurotoxicity. However, there is also evidence for the protection of neurons from stress following hyper-activation of Glu synaptic transmission. Such neuro-protection is mediated through synaptic Glu receptors and involves receptor-activated calcium signaling. However, the molecular pathways beyond the calcium-induced activation of transcription factors have yet to be fully defined. We observed [Badawi et al., Neurosci. Res. 2015, 93, 623-632] that hyper-glutamatergic synaptic activity in the brain of transgenic (Tg) mice that over-express glutamate dehydrogenase (Glud1) only in neurons [Bao et al., J. Neurosci. 2009, 29,13929-13944], can protect neurons following ischemia-reperfusion. To understand the molecular mechanisms for such neuroprotection, we probed for post-transcription mechanisms that might offer resistance to ischemia-reperfusion. We report that following ischemia the Tg mice have increased protein levels of the ATP-inhibited K+ channel (KCNJ1). Increases in the function of these channels in mitochondria protect cardiac and neuronal cells from ischemia/hypoxia. We identified a potential link to over-expression of KCNJ1 being the hypoxia-inducible factor 1a (HIF1a). Either induction of an hypoxia-like state or over-expression of HIF1a in cells in culture, led to increases in the expression of KCNJ1. We identified consensus sequences for HIF1a binding in the KCNJ1 promoter that are linked to the transcriptional activation by HIF1a. We recently also identified potential sites for epigenomic regulation of HIF1a and will continue to probe how these sites may be related to the effects of a hyper-glutamatergic state. Based on our observations, we advance the hypothesis that chronic increases in Glu synaptic transmission lead to increases in the expression of K+ channels in mitochondria and these increases are produced through upstream induction or stabilization of HIF1a, a transcription factor known to protect cells against many stresses. [Supported by grants AG012993 and AG035982 from the Nat. Inst. on Aging]

Disclosures: **E.K. Michaelis:** None. **D. Hui:** None. **R. Pal:** None. **M.L. Michaelis:** None. **X. Wang:** None.

Poster

572. Neurotrophins

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 572.01/B34

Topic: B.01. Neurotransmitters and Signaling Molecules

Title: Functions of novel RET isoforms in the nervous system

Authors: ***N. A. GABRESKI**[1], S. S. NOVAKOVA[2], J. VAGHASIA[2], B. A. PIERCHALA[1]; [1]Cell. and Mol. Biol. Grad. Program, [2]Biologic and Materials Sci., The Univ. of Michigan, Ann Arbor, MI

Abstract: Ret, a receptor tyrosine kinase that is activated by the glial cell line-derived neurotrophic factor (GDNF) family ligands (GFLs), plays a crucial role in the development and function of the nervous system, and additionally has important roles in kidney development and spermatogenesis. *RET* encodes a transmembrane receptor that is 20 exons long and produces two known protein isoforms differing in C-terminal amino acid composition, referred to as RET9 and RET51. Studies of human pheochromocytomas identified an additional two novel transcripts involving the skipping of exon 3 or exons 3, 4, and 5 and are referred to as $RET^{\Delta E3}$and $RET^{\Delta E345}$, respectively. Our analysis has revealed that these *RET* transcripts are also expressed in normal tissues of zebrafish, mice, rats and humans. Using reverse transcription PCR (RT-PCR) we have found that both splice variants are expressed in a wide array of tissues and at different ages in mice, and that these transcripts can have either a *Ret9* or *Ret51* c-terminal tail creating increased diversity of potential Ret proteins. The $RET^{\Delta E3}$ and $RET^{\Delta E345}$ isoforms are predicted to encode full-length Ret proteins with deletions in the extracellular domain, but their functional significance has not been established. Our *in vitro* analysis has shown that these proteins can interact with all four GFRα co-receptors, and that $RET51^{\Delta E3}$ can function as a GFL receptor while $RET51^{\Delta E345}$ can inhibit full-length RET51 activation. We are continuing experiments to identify the presence and the functions of these isoforms *in vivo*, particularly during development.

Disclosures: **N.A. Gabreski:** None. **S.S. Novakova:** None. **J. Vaghasia:** None. **B.A. Pierchala:** None.

Poster

572. Neurotrophins

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 572.02/B35

Topic: B.01. Neurotransmitters and Signaling Molecules

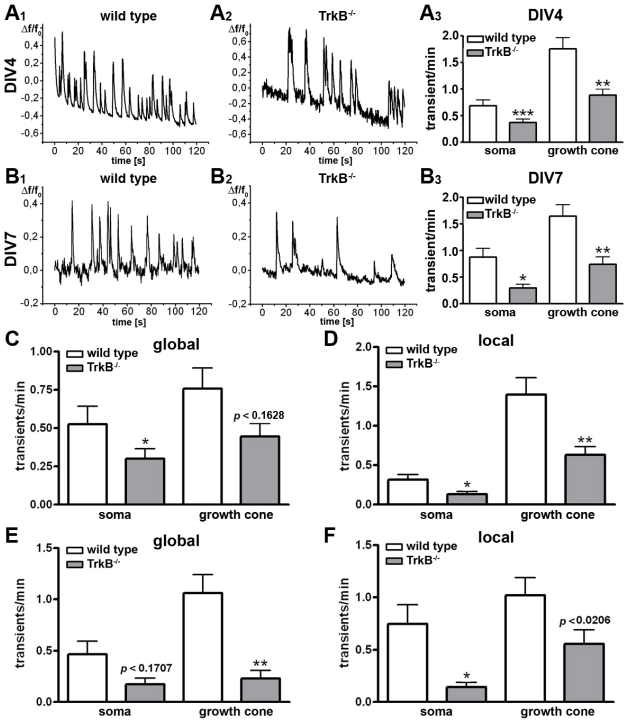
Support: DFG BL567 to R.B.

Hermann and Lilly Schilling Stiftung to M.S.

Title: TrkB modulates the function of Nav1.9 in activity-dependent axon growth in developing motoneurons

Authors: *R. BLUM, A. WETZEL, S. SAMTLEBEN, B. DOMBERT, S. JABLONKA, M. SENDTNER;
Univ. of Wuerzburg, Wuerzburg, Germany

Abstract: Embryonic motoneurons exhibit spontaneous electrical activity long before motor axons make synaptic contacts with the skeletal muscle. Spontaneous activity in cultured embryonic motoneurons is initiated by the voltage-gated sodium channel Nav1.9, providing an initial trigger signal for voltage-dependent calcium influx which then promotes activity-dependent axon growth. Several previous reports suggested that Nav1.9 opening may be promoted by the neurotrophin receptor TrkB, but evidence on direct interaction of these transmembrane proteins remained controversial. Here we studied the role of TrkB in spontaneous activity-dependent axon elongation in isolated motoneurons. In TrkB knockout motoneurons, BDNF effects on survival are reduced, but these cells can be supported by the neurotrophic factor CNTF. Interestingly, these TrkB-/- motoneurons exhibited a reduced frequency of spontaneous calcium transients in axons and growth cones, and this effect correlated with reduced axon growth. Similar observations were made with Nav1.9 deficient motoneurons. In order to study how TrkB modulates Nav1.9 in motoneurons, we developed a new mouse model for direct ER calcium imaging in motoneurons and hippocampal neurons. This mouse model should allow to investigate whether local calcium transients are initiated by TrkB signaling which then could lead to activation of Nav1.9 channels and subsequently to enhanced rates of spontaneous calcium influxes for regulation of axon growth, or whether Nav1.9 activation occurs in the absence of TrkB-mediated ER calcium release.



Disclosures: **R. Blum:** None. **A. Wetzel:** None. **S. Samtleben:** None. **B. Dombert:** None. **S. Jablonka:** None. **M. Sendtner:** None.

Poster

572. Neurotrophins

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 572.03/B36

Topic: B.01. Neurotransmitters and Signaling Molecules

Title: Identification of nascent proteins synthesized locally in the axons of cultured rat cortical neurons

Authors: *C.-Y. WU;
Inst. of Systems Neurosci., Natl. Tsing Hua Univ., Taipei, Taiwan

Abstract: Local protein synthesis has been proposed to play important roles in the growth, navigation and synaptogenesis of axons. More recently, it has been found that exposures to brain-derived neurotrophic factor (BDNF) and glutamate enhance local protein synthesis in the axons which have been severed from their cell bodies of rat cortical neurons in culture. Here, we

use MS spectrometric methodologies to identify the nascent proteins synthesized in axons without or with being subjected to glutamate or BNDF stimulation. We use bioorthogonal noncanonical amino acid tagging (BONCAT) method to label the nascent proteins in severed axons with biotin functional groups under various conditions. Proteins in the lysis of the axons are subjected to exhaustive trypsin digestion, and biotinylated peptides are pulled down by streptavidin beads. The collected peptides are then subjected to LC/MS/MS identification. A quantitative, comparative analysis among the nascent proteins locally synthesized in cortical axons without subjected to any stimulation and upon stimulation with glutamate and BDNF is also carried out. The above results will be presented in the poster. Our results will shed lights to how local protein synthesis may contribute to the various functions of axons at the basal level and upon exposure to stimulation with glutamate and BDNF.

Disclosures: C. Wu: None.

Poster

572. Neurotrophins

Location: Hall A

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Program#/Poster#: 572.04/B37

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: 2014SGR0344

2014PFR-URV-B2-83

Title: BDNF and TrkB are regulated by both pre- and postsynaptic activity and enhance presynaptic cPKC-betaI to modulate neuromuscular synaptic function

Authors: *M. A. LANUZA, E. HURTADO, L. NADAL, T. OBIS, A. SIMON, V. CILLEROS, N. GARCIA, M. M. SANTAFÉ, M. TOMÀS, J. TOMÀS;
Univ. Rovira i Virgili, Reus, Spain

Abstract: In the last few years, it has shown increasing evidence that one of the benefits of physical activity/exercise on the health of the CNS is to improve the synaptic function (Van Praag-H et al., 1999). Additionally, it is well accepted the preponderance of BDNF in mediating these benefits (reviewed by Gomez-Pinilla and Hillman, 2013). However, how an increase of synaptic activity-induced muscle contraction can modulate crucial aspects of neuromuscular synaptic function through BDNF and its receptor, TrkB, remains unknown. We have recently identified that PKC family is involved in neurotransmitter release when continuous electrical

stimulation imposes a moderate activity on the NMJ and that muscle contraction has an important impact on levels of presynaptic PKC isoforms, such as cPKCbetaI and nPKCepsilon (Besalduch et al., 2010; Obis et al., 2015). Accordingly, the present study is designed to test the hypothesis that muscle contraction is a key regulator of BDNF/TrkB signaling pathway activating presynaptic cPKC isoforms to modulate synaptic function. Results from ELISA and Western blotting techniques support that pre- and postsynaptic neuromuscular activity are both responsible for the increase of BDNF levels in the skeletal muscle (but not NT4) and that nerve induced-muscle contraction regulates TrkB-T1 without affecting TrkB-FL and p75 levels. Furthermore, our results show an involvement of BDNF induced by pre- and postsynaptic activity on regulation of the presynaptic classical cPKC isoforms (alpha and betaI) acting by a signaling pathway through TrkB. We use immunohistochemistry and confocal microscopy to demonstrate that cPKCbetaI is exclusively located in the motor nerve terminals on the NMJ. We also report by electrophysiological techniques and using a cPKCbetaI-specific translocation inhibitor peptide (betaI-V5-3) that cPKCbetaI is decisively involved in ACh release induced by electrical stimulation. Together, these results provide a mechanistic insight into how synaptic activity-induced muscle contraction could regulate the BDNF/TrkB signaling at the NMJ by enhancing BDNF production and decreasing the TrkB-T1 levels. It further suggests that this signalling pathway could increase presynaptic level of the cPKCbetaI isoform to affect neuromuscular neurotransmission.

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Poster

572. Neurotrophins

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Program#/Poster#: 572.05/B38

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: This work was kindly supported by the Eunice Kennedy Shriver NICHD Intramural Research Program, NIH.

Title: Dopamine function in ErbB4 mutant mice

Authors: ***M. SKIRZEWSKI**, I. KARAVANOVA, A. BUONANNO;
Section Mol. Neurobio., NIH/NICHD, Bethesda, MD

Abstract: Single nucleotide polymorphisms and a microdeletion in the genes encoding Neuregulin-1 (NRG1) and its receptor ErbB4, respectively, have been associated with schizophrenia (SZ), a neuropsychiatric disorder characterized by imbalances in brain dopamine (DA) function. Dysfunctional NRG1-ErbB4 signaling in brain areas such as hippocampus, pre-frontal cortex (PFC) and dorsal striatum may contribute to alterations in DA function, which in turn may explain several symptoms related to SZ. In addition, the number of parvalbumin (PV)-expressing fast-spiking basket cells, which also express ErbB4, are reduced in the postmortem dorsal PFC of schizophrenia patients and are implicated in the reduction of evoked gamma oscillations associated with cognitive deficits. We previously demonstrated that ErbB4 activation by NRG1 acutely increases extracellular DA levels in the rodent hippocampus, and regulates synaptic plasticity and local network activity by signaling through DA D4 and ErbB4 receptors (Kwon et al. (2008) PNAS 105:15587-92; Andersson et al. (2012) PNAS 109:13118-23). We also showed that NRG1 signals through a mechanism that requires both D4 and ErbB4 receptors to increase the power of kainate-induced gamma oscillations in hippocampal slices. Interestingly, both ErbB4 null and PV interneuron-restricted (PV-Cre;ErbB4f/f) mutant mice share several behavioral deficits with relevance to SCZ (Shamir et al. (2012) J Neurosci. 32:2988-97). The expression of ErbB4 in cortical interneurons and mesocortical/nigrostriatal tyrosine hydroxylase (TH) expressing DA neurons, which send efferent projections to the hippocampus, PFC and striatum, raises the question of the role NRG1/ErbB4 signaling in different neuronal sub-populations. Here we present preliminary experiments resolving behavioral and neurochemical differences between PV interneuron, TH-restricted or null ErbB4 mutant mice. This work was kindly supported by the Eunice Kennedy Shriver NICHD Intramural Research Program, NIH.

Disclosures: **M. Skirzewski:** None. **I. Karavanova:** None. **A. Buonanno:** None.

Poster

572. Neurotrophins

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 572.06/B39

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: CIMO Fellowship

Title: Phenotypic assessment of mice with a loss of TrkB in serotonergic neurons

Authors: *A. STEINZEIG / SHTEINTCAIG, M. PRIYADARSHINI SAHU, E. CASTRÉN; Neurosci. Ctr., Neurosci. Center, Univ. of Helsinki, Helsinki, Finland

Abstract: Growing evidence indicates neurotrophins - factors providing neuronal growth and survival during development - are involved in pathophysiology of mood disorders (Nestler et al., 2002). Antidepressants, namely serotonin reuptake inhibitors increase brain level of brain-derived neurotrophic factor (BDNF) expression and the activation of its receptor TrkB, whereas altered BDNF level affect antidepressants action. Despite the evidence for interaction between BDNF-TrkB and serotonergic system (Martinowich&Lu, 2008), the mechanisms are poorly understood. To examine impact of TrkB receptor to the function of serotonergic system, we used the Cre/loxp system to delete TrkB from serotonergic neurons in a time-specific manner. We crossed two knockout mice strains: $Tph2^{CreERT2}$ and $TrkB^{loxP/loxP}$, to obtain $Tph2^{CreERT2}$:$TrkB^{loxP/loxP}$ mutants. In $Tph2^{CreERT2}$ strain, injections of tamoximen induce Cre-recombination selectively in serotonergic neurons. To induce Cre-mediated TrkB excision tamoxifen was administered 2 mg/mice daily for 5 days starting from PD42-45. Control group received similar course of corn oil injections. Group of $TrkB^{loxP/loxP}$ mice injected with tamoxifen served as an additional control. To confirm the specificity and efficacy of Cre-recombination we used $tdTomato^{loxP/loxP}$: $Tph2^{CreERT2}$ mice, expressing tdTomato fluorescent protein solely in the *Tph2*-positive serotonergic neurons in the raphe nuclei. Immunohistochemical staining revealed co-localization of Cre-positive and tdTomato-positive cells. Furthermore our results indicated that recombination was more efficient in males as compared to the females, therefore only males were used for our experiments. To study behavioral phenotype of the $Tph2^{CreERT2}$:$TrkB^{loxP/loxP}$ mice, we performed the tests for anxiety-like behavior: Light-dark, Forced swim test, Open field and Elevated plus maze after one month post tamoxifen injections. At the time-point investigated, mutant mice exhibit no remarkable behavioral differences as compared to the control animals. The weights of the animals were monitored before and after injections. There was no significant change between groups. Anxiety- and depression-like behaviors may not be triggered by deficits in BDNF/TrkB signaling alone, but rather, may require impairments in several other pathways. Our present model has no major behavioral effect, but a thorough study on other inter-related signaling pathways needs to be done. The interaction of these two major signaling pathway requires further investigation.

Disclosures: A. Steinzeig / Shteintcaig: None. **M. Priyadarshini Sahu:** None. **E. Castrén:** None.

Poster

572. Neurotrophins

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 572.07/B40

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grant F30 DE023479-02

Title: A p75/Ret complex mediates programmed cell death in sympathetic neurons

Authors: *C. R. DONNELLY, N. A. GABRESKI, O. R. STEPHENS, M. A. CHOWDHURY, B. A. PIERCHALA;
Biologic and Materials Sci., Univ. of Michigan, Ann Arbor, MI

Abstract: Target-derived neurotrophic factors, such as the neurotrophins and the glial cell-line derived neurotrophic factor (GDNF) family of ligands (GFLs) are crucial components aiding in the establishment of proper connections between neurons and their targets. In the peripheral nervous system (PNS), GFLs signal through their common receptor tyrosine kinase, Ret, to produce signals critical for neuronal survival, migration, and axonal growth. Recently, we have discovered that Ret associates with p75, a member of the tumor necrosis factor family of death receptors, in transfected cells *in vitro* and in brain, spinal cord, dorsal root ganglion sensory neurons, and superior cervical ganglion sympathetic neurons *in vivo*. This interaction is surprising because p75 is a critical mediator of apoptosis upon activation by proneurotrophins, while Ret is canonically involved in pro-survival signaling as a receptor for the GFLs. Interestingly, the interaction between p75 and Ret was increased upon stimulation of sympathetic neurons with brain-derived neurotrophic factor (BDNF) and proBDNF, both of which induce p75-dependent apoptosis in sympathetic neurons. These findings suggest a functional role of Ret in p75-mediated pro-apoptotic signaling. Consistent with this hypothesis, we find that knockdown of Ret in sympathetic neurons *in vitro* results in a reduction in BDNF-mediated apoptosis and a reduction in p75/BDNF-mediated activation of apoptotic effectors, including phospho-c-Jun and phospho-JNK. Furthermore, we find that genetic deletion of Ret results in a decrease in programmed cell death *in vivo*. Collectively, these data implicate Ret as a novel co-receptor for p75-mediated apoptosis. We suggest that these findings could have important implications for the mechanisms underlying the pathogenesis of gain-of-function mutations in RET resulting in Hirschsprung's disease in humans, and could more broadly have implications for the mechanisms governing apoptosis observed in many neurodegenerative disorders. Ongoing experiments are aimed at identifying the precise mechanism by which Ret is required for p75-mediated apoptosis, as well as the generalizability of this pro-apoptotic signaling complex in other neuronal populations.

Disclosures: C.R. Donnelly: None. **N.A. Gabreski:** None. **O.R. Stephens:** None. **M.A. Chowdhury:** None. **B.A. Pierchala:** None.

Poster

572. Neurotrophins

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Program#/Poster#: 572.08/B41

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: 5R21 AG031267

5R01 AG041944

Title: A time course of inflammation-driven changes in synaptic plasticity: the combined effects of aging and an immune challenge lead to long-lasting deficits in L-LTP in hippocampal area CA1

Authors: *N. TANAKA[1], G. P. CORTESE[2], R. M. BARRIENTOS[3], S. F. MAIER[3], S. L. PATTERSON[1];
[1]Biol., Temple Univ., Philadelphia, PA; [2]Dept. of Pathology and Cell Biol., Columbia Univ., New York, NY; [3]Dept. of Psychology and Neurosci., Unversity of Colorado, Boulder, CO

Abstract: Aging significantly increases brain vulnerability to negative life events. Cognitive function in older individuals often declines precipitously after events (surgery, infection, or injury) that trigger activation of the peripheral immune system. Even if the decline is temporary, its occurrence is associated with an increased probability of eventually developing dementia. Very little is known about the underlying mechanisms, but a rodent model offers some clues. Aged (24-month-old) Fischer Brown Norway (F344xBN) rats generally do not show significant physical or cognitive impairments. However, in response to signals triggered by a peripheral immune challenge (an intraperitoneal injection of E. coli), they mount an exaggerated inflammatory response in the brain. Their hippocampi produce more of the pro-inflammatory cytokine interleukin-1beta (IL-1β), and produce it longer than those of their younger (3-month-old) counterparts (Barrientos et al., 2009). In the aging animals, hippocampal IL-1β levels are significantly elevated 4 hours after infection and remain so for at least 8 days, but generally less than 14 days; in contrast, levels in young animals rise in response to infection but return to near basal levels within 24 hours. Interestingly, the prolonged elevation in IL-1β in aged animals is paralleled by prolonged, specific deficits in hippocampus-dependent long-term memory tasks. We have previously demonstrated that a memory related-form of long-lasting synaptic plasticity - theta burst-evoked late-phase long-term potentiation (L-LTP) - is reduced in the aged animals 4 days after the infection (Chapman et al., 2010). We have also reported that levels of the mature brain-derived neurotrophic factor (mBDNF) (the protein isoform thought to be required for long-term forms of memory and LTP) are reduced in aged rats at the same 4 day time point (Cortese et al., 2011). Here we extend these observations, and find that like the deficits in memory, the deficits in theta-burst L-LTP and mBDNF persist for the duration of the elevation in IL-1β.

These results are consistent with the hypothesis that an exaggerated brain inflammatory response, arising from aging and a secondary immune challenge, may be associated with a diminished capacity to provide the BDNF needed for stabilization of memory-related plasticity at synapses in the hippocampus. This also suggests the possibility that dysregulation of immune function may contribute to dysregulation of BDNF-dependent synaptic plasticity in a variety of conditions with an inflammatory component (Ex. autoimmune disorders, depression, PTSD, autism spectrum disorders).

Disclosures: N. Tanaka: None. **G.P. Cortese:** None. **R.M. Barrientos:** None. **S.F. Maier:** None. **S.L. Patterson:** None.

Poster

572. Neurotrophins

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 572.09/B42

Topic: B.01. Neurotransmitters and Signaling Molecules

Title: Stimulus-specific combinatorial functionality of neuronal c-fos enhancers

Authors: *J.-Y. JOO, T.-K. KIM;
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Abstract: The c-fos gene is induced by a broad range of stimuli, and has been commonly used as a reliable marker for neural activity. Its induction mechanism and available reporter mouse lines are exclusively based on the c-fos promoter activity. Here, we demonstrate that multiple enhancers surrounding the c-fos gene are critical for ensuring robust c-fos response to various stimuli. Membrane depolarization, brain-derived neurotrophic factor (BDNF), and Forskolin activate distinct subsets of the enhancers to induce c-fos transcription in neurons, suggesting that stimulus-specific combinatorial activation of multiple enhancers underlies the broad inducibility of the c-fos gene. Accordingly, the functional requirement of key transcription factors varies depending on the type of stimulation. Combinatorial enhancer activation also occurs in the brain. Providing a comprehensive picture of the c-fos induction mechanism beyond the minimal promoter, our study should help in understanding the physiological nature of c-fos induction in relation to neural activity and plasticity

Disclosures: J. Joo: None. **T. Kim:** None.

Poster

572. Neurotrophins

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 572.10/B43

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: JSPS KAKENHI Grant 24500619

Title: Inhibition of GABAregic synapses removes exercise-induced expression of nerotrophins in the motor cortex

Authors: *H. MAEJIMA[1], N. KANEMURA[2];
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Abstract: Neurotrophins positively modulate neuronal survival and plasticity in the brain. Physical exercise up-regulates the expression of neurotrophins including BDNF and NT-4 in the brain. GABAA is the most common neurotransmitter associated with IPSP in the brain. Recent reports indicate that the inhibition of GABAregic synapses in the hippocampus enhances neural plasticity associated with the increased expression of BDNF. The objective of the present study was to investigate the effects of exercise and the inhibition of GABAegic synapses on the expression of neurotrophins in the mouse motor cortex. ICR mice at 15 weeks of age were assigned to four groups based on two factors (exercise and the inhibition of GABAregic synapses). The mice in the exercise groups performed moderate treadmill exercise (15 m/min, 60 min) every day. The inhibition of GABAregic synapses was induced by intraperitoneal administration of GABAA receptor antagonist (picrotoxin, 1mg/kg). The intervention composed of exercise and picrotoxin administration was continued for 10 days. After the intervention, the motor cortex was deprived for quantitative PCR analyses. The mRNA expression of neurotrophins (BDNF and NT-4), and TrkB receptor of BDNF and NT-4 in motor cortex was measured based on real time PCR. Additionally, the expression of c-fos was measured as a maker of neural activity. All procedures were approved by the ethics committee for animal research of Saitama Prefectural University. After the intervention for 10 days, where exercise significantly increased the expression of BDNF and NT-4, picrotoxin administration to sedentary mice showed no effect on the expression of tneurotrophins. On the contrary, picrotoxin administration to exercised mice significantly decreased the expression of BDNF and NT-4 to the level of sedentary mice, indicating that picrotoxin administration removed the exercise-induced up-regulation of BDNF and NT-4. Interestingly, c-fos expression was also significantly decreased by picrotoxin administration in exercised mice. There was no effect of exercise and picrotoxin administration on the expression of TrkB. Taken together, the present study elucidated

that GABAA receptor blockade negatively modifies exercise-induced up-regulation of neurotrophins and neural activity in the motor cortex. It was suggested that, unlike the positive modification by GABAA receptor blockade in the hippocampus, exercise in the presence of regulated neuronal balance between EPSP and IPSP is crucial for the up-regulation of neural activity and the expression of neurotrophins in the motor cortex.

Disclosures: H. Maejima: None. **N. Kanemura:** None.

Poster

572. Neurotrophins

Location: Hall A

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Program#/Poster#: 572.11/B44

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: MIUR (PRIN 2010N8PBAA)

Title: Physical exercise-induced improvements of behavior and neuroplasticity are impaired in the BDNF Val66Met knock-in mice

Authors: A. IERACI[1], A. I. MADAIO[1], *A. MALLEI[1], F. S. LEE[2], M. POPOLI[1];
[1]Univ. degli Studi di Milano, Milano, Italy; [2]Dept. of Psychiatr, Cornell Univ., New York, NY

Abstract: Several lines of evidence suggest that physical exercise (PE) is an affordable and effective method to improve cognitive functions and mood at all ages, even in the elderly. Positive effects of PE have been associated with enhanced neuroplasticity, hippocampal neurogenesis and increased levels of brain-derived neurotrophic factor (BDNF). However, a considerable variability of individual responses to PE has been reported. The reason for this is not known, but may be accounted for by individual genetic variants. A common single nucleotide polymorphism (SNP) has been identified in the BDNF human gene (BDNF Val66Met) that leads to decreased BDNF secretion and has been associated with cognitive impairment and mood disorders. Recently, a knock-in mouse carrying BDNF Val66Met polymorphism, which reproduces core phenotypes identified in Val66Met human carriers, has been generated. Despite the well-documented role of BDNF as mediator of the beneficial effects of PE, it is presently unknown whether the BDNF Val66Met SNP influences the degree to which an individual may benefit from PE. To study whether and how the BDNF Val66Met polymorphism impacts the neurobiological effects induced by PE, we evaluated behavioral changes, hippocampal neurogenesis modifications and gene expression variations induced by 4 weeks of voluntary running in wild type ($BDNF^{Val/Val}$) and homozygous BDNF Val66Met

knock-in ($BDNF^{Met/Met}$) male mice. We found that PE decreased the latency to feed in the novelty suppressed feeding and the immobility time in the forced swimming test in $BDNF^{Val/Val}$ but not $BDNF^{Met/Met}$ mice. PE-induced hippocampal neurogenesis was reduced in $BDNF^{Met/Met}$ mice compare to $BDNF^{Val/Val}$ mice. PE significantly increased total BDNF mRNA, BDNF spliced variants 1, 2, 4, 6 and mGluR2 in the dentate gyrus of $BDNF^{Val/Val}$ but not in $BDNF^{Met/Met}$ mice. $BDNF^{Met/Met}$ mice had lower basal BDNF protein levels in the hippocampus that did not increase following PE treatment. Overall these results showed that the BDNF Val66Met polymorphism impairs the beneficial behavioral and neuroplasticity effects induced by PE in adult male mice.

Disclosures: **A. Ieraci:** None. **A.I. Madaio:** None. **A. Mallei:** None. **F.S. Lee:** None. **M. Popoli:** None.

Poster

572. Neurotrophins

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 572.12/B45

Topic: B.01. Neurotransmitters and Signaling Molecules

Title: Probing the novel relationship between a transcriptional regulator of the cell cycle, Late Simian Virus 40 Factor, neurogenesis and epilepsy

Authors: *K. HOKENSON[1,2,3], U. HANSEN[4], A. R. BROOKS-KAYAL[5], S. J. RUSSEK[1,2,3]; [1]Pharmacol. and Exptl. Therapeut., [2]Program in Biomed. Neurosci., [3]Lab. of Translational Epilepsy, Boston Univ. Sch. of Med., Boston, MA; [4]Biol., Boston Univ., Boston, MA; [5]Pediatrics, Div. of Neurol., Univ. of Colorado Denver - Anschutz Med. Campus, Denver, CO

Abstract: Epilepsy is a neurological condition that causes recurrent, unprovoked seizures and is poorly understood. Our lab previously established a role for brain-derived neurotrophic factor (BDNF) in epilepsy, through regulation of GABAR subunits through activation of the Janus kinase (JAK)/Signal Transducer and Activators of Transcription (STAT) pathway. The pathophysiology of some types of epilepsy is thought to involve neurogenesis, the formation of new neurons from progenitor cells, in the dentate gyrus of the hippocampus. Late Simian Virus 40 Factor (LSF) is a transcription factor that plays a ubiquitous role in regulating cell cycle progression and cell survival and has been implicated in a number of diseases, including Alzheimer's disease (AD). The major site of phosphorylation by Erk on LSF is serine 291, while transient phosphorylation occurs at serine 309 by cyclin C/CDK2, in early G1. As cells progress through G1, LSF is dephosphorylated at both sites, and phosphorylation by Erk and cyclin

C/CDK2 at the G0/G1 transition down-modulates the activity of LSF during passage through G1. Our studies were designed to examine the role of LSF in neurons with the promise of learning more about neurogenesis and its role in epileptogenesis. We found that BDNF induced the phosphorylation of LSF at serine 291 in hippocampal and cortical primary neuron cultures, while levels of total LSF or p309 LSF did not change. *In vivo,* we found increased phosphorylation of p291 LSF in the hippocampus of rats with pilocarpine-inducted model of status epilepticus (SE), compared to control rats. Potassium chloride (KCl; 20mM for 2 hours) treatment did not affect phosphorylation of LSF at serine 291 LSF at days 7 or 14 *in vitro*. Using immunocytochemistry, we co-labeled with NeuN, a neuronal marker, and either total LSF, p291 LSF, or p309 LSF, and found that all forms of LSF are present in cortical and hippocampal neurons. Using Click-It EdU kit to label proliferating cells, we found decreased levels of p291 LSF within proliferating cells. EdU-positive neurons co-labeled for Nestin, but did not co-label for MAP2. Comparing protein levels of p291 LSF in adult brain regions that are relevant to neurogenesis, we found levels of p291 LSF differed significantly between the cortex, hippocampus, and olfactory bulb. Olfactory bulb had the highest levels, followed by hippocampus, while cortex had the lowest levels of p291 LSF. Cortex contained only one p291 LSF protein band, while hippocampus and olfactory bulb contained two p291 LSF protein bands near 63 kDa. Our results suggest that LSF phosphorylation may be mediated by BDNF signaling, which could potentially influence neurogenesis and epileptogenesis.

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Poster

572. Neurotrophins

Location: Hall A

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Topic: B.01. Neurotransmitters and Signaling Molecules

Support: University Medical School of Catania (Departmental Project)

Alzheimer's Association (IIRG-09-134220)

IRCCS Oasi Maria SS. Troina (RC-02-01; RC-06-08)

Title: Physiological role of TGF-β1 in hippocampal synaptic plasticity and memory

Authors: *D. PUZZO, W. GULISANO, C. A. GUIDA, A. A. R. IMPELLIZZERI, F. DRAGO, A. PALMERI, F. CARACI;
Univ. of Catania, Catania, Italy

Abstract: Transforming Growth Factor β1 (TGF-β1) is a cytokine involved in the control of cell growth, differentiation as well as immune suppression and repair after injury. In addition to its well-known neuroprotective and neurotrophic properties, it has been recently reported a possible role of TGF-β1 in synaptic transmission. However, its involvement in physiological mechanisms underlying synaptic plasticity and memory at hippocampal level has not been thoroughly investigated. Here, we aimed to examine the role of TGF-β1 in hippocampal long-term potentiation (LTP) and memory in adult wild type mice. For this purpose, we first performed electrophysiological studies to assess the effect of exogenous TGF-β1 on CA1 LTP and phosphorylation of the transcription factor cAMP-Responsive Element Binding protein (CREB). Then, we investigated the role of endogenous TGF-β1 in hippocampal synaptic plasticity, recognition memory and phospho-CREB levels by blocking its signaling pathway with SB431542, a selective inhibitor of the activin-like kinase (ALK) 5 TGF-β type I receptor. Finally, we examined the involvement of p-SMAD2, a TGF-β1 downstream pathway effector. We found that administration of exogenous TGF-β1 was able to convert early-phase-LTP into late-phase-LTP. Furthermore, the block of the endogenous TGF-β1 signaling pathway by SB431542, impaired LTP and object recognition memory. The latter impairment was rescued by administration of exogenous TGF-β1. TGF-β1 functional effects correlated with an increased expression of the phospho-CREB. Moreover, SB431542 selectively inhibited both the phosphorylation of SMAD2 and p-CREB, which was rescued by TGF-β1 treatment, thus suggesting a similar trend between p-SMAD2 and p-CREB levels. These findings suggest that endogenously produced TGF-β1 plays a key role in physiological mechanisms underlying LTP and memory.

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Poster

572. Neurotrophins

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 572.14/B47

Topic: B.01. Neurotransmitters and Signaling Molecules

Title: Generation and characterization of a brain derived neurotrophic factor (BDNF rs6265) knockin rat

Authors: *C. E. SORTWELL, C. J. KEMP, J. W. LIPTON, A. COLE-STRAUSS, F. P. MANFREDSSON, N. M. KANAAN, M. F. DUFFY, N. MARCKINI, T. J. COLLIER; Translational Sci. and Mol. Med., Michigan State Univ., Grand Rapids, MI

Abstract: A highly prevalent variant in the brain derived neurotrophic factor (BDNF) gene exists in the general population (rs6265: val66met 35.4%, met66met 5.2%). Both the heterozygous major allele and homozygous minor allele of BDNF rs6265 result in a disruption of packaging and release of activity-dependent BDNF, whereas constitutive release of BDNF is unaffected. In humans, BDNF rs6265 variant status has previously been shown to impact grey matter volume during aging, memory performance, obesity, anxiety and depression as well as influence the therapeutic efficacy of antidepressants and antipsychotics. Further, we have previously shown that rs6265 allele status impacts rate of symptom progression in early, unmedicated Parkinson's disease subjects as well as response to anti-parkinsonian medication. Existing transgenic BDNF val66met and met66met mice recapitulate many of the human features associated with this variant however a rat model of BDNF rs6265 would offer distinct advantages. Rats have more complex cognitive and motor behaviors and are more similar to humans in their genetics and pharmacokinetics than mice, suggesting that results of therapeutics tested in rats would provide greater predictive validity than mice. The greater synaptic complexity observed in the rat brain compared to mice indicates that neural plasticity may be better modeled in the rat. On a practical level, the larger brain and body size of the rat allows researchers to harvest more tissue and fluid samples, enables neurosurgical interventions and *in vivo* electrophysiology, facilitates intrathecal drug delivery and can allow for neuroimaging procedures that can be more difficult in mice. With these advantages of the rat in mind, we generated a val68met BDNF knockin rat (corresponds to human val66met due to two additional Thr in rat Bdnf at positions 57 and 58) using nuclease-mediated genome editing technology (Cyagen). Two val68met founder females were generated on the Sprague Dawley background and have been successfully bred to homozygosity. BDNF val68val, val68met and met68met genotype has been verified via custom-designed TaqMan SNP genotyping assay. No breeding issues have arisen and both heterozygous and homozygous rat pups are viable and healthy for at least 6 months. Ongoing studies will examine the integrity of the nigrostriatal system as well as whole tissue and depolarization-dependent BDNF levels. This novel rat model can serve as a platform for studying the role of this prevalent BDNF rs6265 single nucleotide polymorphism in neurological disease and therapeutic mechanisms.

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Poster

572. Neurotrophins

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Topic: B.01. Neurotransmitters and Signaling Molecules

Support: Ministry of Education Academic Research Fund Tier 2 (MOE2012-T2-1-021)

Title: Loss of brain-derived neurotrophic factor (BDNF) signalling in cortico-limbic interneurons contributes to synaptic imbalance and abnormal social behaviour in mice

Authors: *S. TAN[1,2,3], Y. XIAO[1], Y.-C. YEN[1], H. YIN[4], T. W. SOONG[3], H. S. JE[1,3];
[1]Duke-NUS Grad. Med. Sch., Singapore, Singapore; [2]NUS Grad. Sch. for Integrative Sci. and Engin., Singapore, Singapore; [3]Yong Loo Lin Sch. of Medicine, Natl. Univ. of Singapore, Singapore, Singapore; [4]Duke Inst. for Brain Sci., Durham, NC

Abstract: The execution of complex behaviour is dependent on the establishment of a tight balance between inhibition and excitation in cortico-limbic circuits of the mammalian brain. Developmental disruptions to either component have been implicated in neuropsychiatric disorders. BDNF is an important trophic factor for the developmental maturation of inhibitory neurons and their synaptic transmission. Due to the lack of genetic knockout mouse models, behavioural consequences of impaired BDNF signaling in cortico-limbic inhibitory neurons have not been elucidated. Therefore, we generated conditional knockout mice in which tropomyosin receptor kinase B (TrkB), the cognate receptor for BDNF, is ablated from a subset of cortico-limbic interneurons. Although their motor coordination and movement were not impaired, these mice exhibited abnormal social behaviour. Furthermore, electrophysiological analysis revealed an imbalance between excitatory and inhibitory neurotransmission within layer V local microcircuit of the prelimbic area in these mice. Taken together our results suggest a critical role of cortico-limbic interneuron BDNF-TrkB signalling in complex social behaviour. Disruptions to this pathway may underlie some of the abnormal behaviour present in neuropsychiatric disorders.

Disclosures: S. Tan: None. **Y. Xiao:** None. **Y. Yen:** None. **H. Yin:** None. **T.W. Soong:** None. **H.S. Je:** None.

Poster

572. Neurotrophins

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Topic: B.01. Neurotransmitters and Signaling Molecules

Support: Latham Foundation and startup funds from Howard University

NIA/NIH HUADAR1R25AG047843-01

Title: BDNF levels mediate constitutive activity of ERα and ERβ, but not GPER in neuro-2A cells

Authors: *B. O. OGUNLADE[1], M. R. DESHOTELS[2], E. SPINU[2], A. G. ROBINSON[3], K. MANAYE[4], C. M. FILIPEANU[5];
[1]Howard Univeersity, Washington, DC; [2]Dept. of Pharmacol. and Exptl. Therapeut. and cardiovascular centre of excellence., Louisiana state Univ., New Orleans, LA; [4]Dept. of Physiol., [5]Dept. of Pharmacol., [3]Howard Univ., Washington, DC

Abstract: The neuroprotective effects of estrogens in CNS are well recognized but the receptors and the signaling pathways underlying these effects remain elusive. To start elucidating these aspects, in the present study we investigated the effects of exogenous expression of the estrogen receptors on neuronal differentiation and signaling of Neuro-2A cells. This cell line was selected because it retains the ability to differentiate toward a neuronal phenotype in presence of appropriate stimuli. Further, we found by both RT-PCR and western blot that Neuro-2A cells do not endogenously express either typical estrogen receptors ERα and ERβ, or the estrogen-related G-protein coupled receptor GPER. Transfection of neuro-2A cells with ERα, ERβ or GPER resulted in a marked increase of the number of cells bearing neuritis (25 ± 6.1%, 31± 8%, and 34±6% respectively, compared to control 15±4%). Surprisingly, treatment with the estrogen receptor ligands 17β-estradiol (100 nM, membrane permeable) and BSA-17β-estradiol (100 nM, membrane impermeable) did not further increase the number of differentiated cells. Also, the estrogen receptor ligand ICI-182,780 (100 nM) was without effect. The expression of ERα, ERβ or GPER was also accompanied by significant enhancement of basal cAMP cellular levels compared to cells transfected with empty vector. Brain derived neurotrophic factor (BDNF) mRNA levels were significantly enhanced by expression of ERα and ERβ, but not by expression of GPER. As in the case of neurite outgrowth experiments, 17β-estradiol, BSA-17β-estradiol and ICI-182,780 do not further change the responses observed after estrogen receptor expression. In conclusion, our results demonstrate that all three estrogen receptor subtypes are involved in neuronal differentiation of Neuro-2A cells. In addition ERα, ERβ and GPER appear to be constitutive active in this cell line, modulating cellular activity in absence of cognate ligands. BDNF is essential in responses induced by typical receptors ERα and ERβ, but not in the effects

of GPER. Supported by Latham Foundation and startup funds from Howard University (to CMF) and NIA/NIH HUADAR1R25AG047843-01 (to KM). Keywords: Estrogen Receptors, Neuronal Differentiation, and BDNF

Disclosures: **B.O. Ogunlade:** None. **M.R. Deshotels:** None. **E. Spinu:** None. **A.G. Robinson:** None. **K. Manaye:** None. **C.M. Filipeanu:** None.

Poster

572. Neurotrophins

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Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grant MH094896

Title: Endocannabinoid-BDNF interactions at cortical excitatory synapses

Authors: ***M. L.-W. YEH**, R. SELVAM, E. S. LEVINE;
Neurosci., Univ. of Connecticut Hlth. Ctr., Farmington, CT

Abstract: Endocannabinoids (eCBs) and neurotrophins, particularly brain-derived neurotrophic factor (BDNF), are potent neuromodulators that are highly expressed throughout the mammalian neocortex. Both eCBs and BDNF play critical roles in many behavioral and neurophysiological processes and are primary targets for the development of novel therapeutics, specifically in relation to depression, anxiety and schizophrenia. In mammalian neocortex, eCBs and BDNF bind primarily to the type 1 cannabinoid receptor (CB1R) and the high affinity trkB tyrosine kinase receptor, respectively. These receptors are expressed throughout the cortical mantle, with the highest levels of both trkB and CB1Rs found in layers II/III and V. Our laboratory and others have previously established that at glutamatergic synapses in these cortical layers, BDNF rapidly potentiates excitatory transmission by enhancing presynaptic glutamate release and modulating NMDA receptors. In contrast, we have recently shown that BDNF attenuates inhibitory transmission by inducing postsynaptic release of eCBs that act retrogradely to suppress GABA release from presynaptic terminals. It is not known whether BDNF also induces release of eCBs at excitatory synapses, which could have a mitigating or opposing effect on the direct effects of BDNF at these synapses. Here, we investigate the physiological interactions between eCBs and BDNF at excitatory synapses in layer V using acute slices from mouse somatosensory cortex. Consistent with previous results, we observed an increase in the frequency but not amplitude of spontaneous AMPA-mediated miniature excitatory postsynaptic currents (mEPSCs) after bath

application of 0.2 nM BDNF. We also observed an increase in mEPSC frequency following exposure to the specific CB1R antagonist SR141716A, suggesting that tonic eCB signaling is present at these terminals. Bath perfusion of BDNF in the presence of SR141716A typically resulted in a greater increase in mEPSC frequency than BDNF alone, suggesting that BDNF-trkB signaling induced the release of eCBs at these excitatory synapses. We are also using immunohistochemistry to examine colocalization of trkB and CB1R at glutamatergic synapses. These observations bolster the growing evidence for cross-talk between eCB and BDNF signaling at cortical synapses.

Disclosures: **M.L. Yeh:** None. **R. Selvam:** None. **E.S. Levine:** None.

Poster

572. Neurotrophins

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 572.18/B51

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grant MH085776 (A.M.)

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Title: SNAREs mediate BDNF secretion essential for the development of callosal axons

Authors: *M. SHIMOJO[1,2], J. COURCHET[3], S. PIERAUT[2], N. TORABI-RANDER[2], M. HIGUCHI[1], F. POLLEUX[3], A. MAXIMOV[2];
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Abstract: Neurons employ a diverse repertoire of trafficking organelles for the secretion of soluble cargo molecules and recycling of membrane constituents, and these mechanisms are essential for the circuit development and functional maintenance of the mammalian brain. Recent studies have identified core components of the secretory machinery that elicit the release of neurotransmitters from presynaptic terminals. Synaptic vesicle exocytosis is mediated by a ternary complex of SNARE (Soluble NSF Attachment Protein Receptor) proteins, represented by

a composition of synaptobrevin/VAMP2 (Syb2), SNAP25 and Syntaxin1, which facilitates membrane fusion. A variety of diffusible peptide cues also appear to be transported by dense core vesicles and undergo exocytosis, supporting the hypothesis that diverse SNAREs independently contribute to different types of membrane fusion. Among such peptide cues, the brain-derived neurotrophic factor (BDNF) is known to play critical roles in the development and homeostatic maintenance of the nervous system. However, the molecular mechanisms that control the secretion of BDNF and other diffusible protein cues remain largely unknown. Here, we demonstrate that, using total internal reflection fluorescence microscopy and BDNF fused to pH-sensitive GFP variant super-ecliptic pHluorin, activity-dependent exocytosis of BDNF from somatodendrites and axons of primary cortical neurons is mediated by SNARE proteins Syb2 and SNAP25, indicating that these SNAREs act in multiple secretory pathways. Importantly, axonal secretion of BDNF is also specifically regulated by SNAP47, one of the uncharacterized neuronal SNARE protein, suggesting this molecule plays as a part of unique SNARE complex fundamental to peptidergic vesicular release. Furthermore, during the development of mouse brain, shRNA mediated knockdown of SNAP47 in layer II/III pyramidal neurons of somatosensory cortex by *in utero* electroporation impairs the targeting and terminal branching of callosal commissure axons *in vivo* with cell-autonomous manner, similar to knockdown of BDNF and its receptor TrkB. Taken together, these novel combinatorial SNARE functions in BDNF secretion provide an important insight for neuronal circuit connectivity and brain development.

Disclosures: **M. Shimojo:** None. **J. Courchet:** None. **S. Pieraut:** None. **N. Torabi-Rander:** None. **M. Higuchi:** None. **F. Polleux:** None. **A. Maximov:** None.

Poster

572. Neurotrophins

Location: Hall A

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Program#/Poster#: 572.19/B52

Topic: B.01. Neurotransmitters and Signaling Molecules

Title: Effects of BDNF, proBDNF and fluvoxamine on NO release from activated rodent microglial cells

Authors: ***Y. MIZOGUCHI**, Y. HARAGUCHI, H. NABETA, Y. IMAMURA, A. MONJI; Dept. Psychiatry, Fac. Medicine, Saga Univ., Saga, Japan

Abstract: Microglia are immune cells which release many factors, including proinflammatory cytokines, nitric oxide (NO) and neurotrophins, when they are activated after the disturbance in

the brain. There is increasing evidence suggesting that pathophysiology of neuropsychiatric disorders is related to the inflammatory responses mediated by microglia. Brain-derived neurotrophic factor (BDNF) is a neurotrophin well known for its roles in the activation of microglia as well as in the pathophysiology and/or the treatment of neuropsychiatric disorders. We have previously reported that pretreatment of BDNF significantly suppressed the release of NO from activated microglial cells, possibly mediated by sustained store-operated calcium entry (SOCE) induced by BDNF. Although BDNF is initially translated as the precursor proBDNF, which binds p75 neurotrophin receptor (NTR), it remains obscure whether proBDNF affects the release of NO from activated microglial cells. We observed that pretreatment of proBDNF significantly potentiated the release of NO from activated microglial cells. RT-PCR and immunocytochemical techniques revealed that p75NTR were highly expressed in rodent microglial cells. Opposite effects of BDNF and proBDNF on microglial function might contribute to the dichotomy of BDNF actions on neuroinflammation and also be involved in the pathophysiology and/or the treatment of neuropsychiatric disorders. In this study, we also tested the effect of fluvoxamine, a potent agonist of sigma-1 receptors, on the intracellular Ca2+ mobilization and function of rodent microglial cells.

Disclosures: **Y. Mizoguchi:** None. **Y. Haraguchi:** None. **H. Nabeta:** None. **Y. Imamura:** None. **A. Monji:** None.

Poster

572. Neurotrophins

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Topic: B.01. Neurotransmitters and Signaling Molecules

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Title: Mesocortical BDNF-mediated disinhibition of mPFC GABA neurons contributes to neuropathic pain

Authors: *F. FENG, W.-Y. SHI, X.-Y. HONG, Y.-Q. LI, J.-X. YANG, H.-R. WANG, L. WANG, X.-Y. WANG, H.-L. DING, H. ZHANG, J.-L. CAO;
Xuzhou Med. Col., Jiangsu, China

Abstract: Neuropathic pain has a 0.9%~17.9% of global prevalence, impairs the quality of life for millions of people. Only 1/3~2/3 of patients benefit from chronic use of currently available analgesics or antidepressants. Increasing evidence shown that neuropathic pain is a neural circuit disorder. The limited understanding of the neural circuitry in the brain involved in neuropathic pain is one of the key reasons for the lack of more effective treatments. mPFC has been implicated in chronic neuropathic pain, and receives heavy synaptic inputs from the ventral tegmental area (VTA), however the downstream cellular target of these synaptic inputs and the underlying molecular mechanisms remain largely unknown. Like most of the nucleus in the brain, medial prefrontal cortex (mPFC) is composed of principal neurons (pyramidal cells) that project to other areas and GABA-ergic interneurons that serve to integrate information among afferents. Here, focusing on mPFC GABA neurons, we first investigated the expression of inhibitory neurotransmitter GABA on day 7 following chronic constrictive injury (CCI) surgery in sciatic nerve, a widely used neuropathic pain model. Our enzyme-linked immunosorbent assay (ELISA) data found a significant decrease of GABA expression in the contralateral mPFC from CCI mice as compared to sham group. Interestingly, we observed that infusion of muscimol, a $GABA_A$ receptor agonist, evoked thermal hyperalgesia in the unaffected hindpaws of CCI mice, but not in sham mice. This result suggests that the contralateral mPFC of CCI mice is under a sub-activation state, and ready to be activated by intrinsic or extrinsic mechanisms that normally not sufficient to evoke behavioral effects. VTA dopamine neuron is a main source of BDNF in mPFC. To identify the role of BDNF in modulating CCI-induced disinhibition of mPFC GABA neurons, we injected AAV-GFP-BDNF to express BDNF in VTA neurons and observed overlap expression of BDNF and GAD65, a molecular mark of GABA neurons. This result built a direct link between VTA-derived BDNF and mPFC GABA neurons. Furthermore, on day 7 after CCI surgery, we infused BDNF into contralateral mPFC, and observed a significant decrease in paw withdrawal latency as well as a decreased expression of GABA and histone H3 acetylation (ACH3) in CCI mice, which could be reversed by pretreatment with Trichostatin A, a histone deacetylase inhibitor. Double immunofluorescent staining also confirmed an overlap expression of ACH3 and GAD. These studies unravel a novel neural circuit and its functional molecular mechanisms in neuropathic pain, and provide highly useful circuit and molecular targets to treat neuropathic pain.

Disclosures: F. Feng: None. **W. Shi:** None. **X. Hong:** None. **Y. Li:** None. **J. Yang:** None. **H. Wang:** None. **L. Wang:** None. **X. Wang:** None. **H. Ding:** None. **H. Zhang:** None. **J. Cao:** None.

Poster

572. Neurotrophins

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 572.21/B54

Topic: B.01. Neurotransmitters and Signaling Molecules

Support: NIH Grant MH095088

Title: Novel pharmacological modulators of Arc/Arg3.1 protein stability

Authors: *J. LALONDE, S. A. REIS, S. J. HAGGARTY;
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Abstract: Accumulating evidence suggest that aberrant activity of specific molecular networks implicated in the control of actin cytoskeleton remodeling and synapse function contributes to the cognitive deficits associated with many neurodevelopmental, psychiatric and neurological disorders. The Activity-Regulated Cytoskeleton-associated protein (Arc, also known as Arg3.1) plays an important role in synaptic plasticity and memory formation. In recent years, different studies have suggested that defect in Arc biology may be contributing to the pathophysiology of Rett's and fragile X syndromes, Alzheimer's disease as well as schizophrenia. Reversing the imbalance in Arc abundance or activity could be a valid treatment option to help ameliorate the cognitive impairments associated with these serious brain disorders. Achieving this goal, however, will require a quasi-complete understanding of signal-dependent Arc expression in neurons and how different classes of pharmacology can influence this process. Currently, we know that Arc expression is concomitantly regulated by a multitude of signaling pathways at the transcriptional, translational and posttranslational levels. To begin understanding better whether and how various drugs available for the treatment of brain disorders are modulating Arc expression, we developed an image-based, high-throughput screening strategy to test systematically how different small-molecules with known or hypothesized CNS activity can influence BDNF-induced Arc protein expression in mouse primary cortical neurons. With this approach, we identified several molecules that strongly potentiate BDNF-induced Arc protein expression and others that completely block this process. Interestingly, most of the compounds in our library with neuroprotective and/or nootropic quality were found to increase levels of Arc protein, while the majority of the drugs with antidepressant and antipsychotic activity were more prone to limit Arc expression. To validate and expand our results, we selected three functionally related compounds that strongly potentiated Arc protein levels in our screen. Using a combination of experimental approaches, we found that these three small-molecules did not mediate their effect by promoting Arc transcription, as expected, but rather favored stability and accumulation of Arc protein. These striking and unpredicted results reveal a new facet about Arc

biology that may be exploitable for the development of novel pharmacological treatments of brain disorders.

Disclosures: **J. Lalonde:** None. **S.A. Reis:** None. **S.J. Haggarty:** None.

Poster

572. Neurotrophins

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Topic: B.02. Ligand-Gated Ion Channels

Support: The National Natural Science Foundation of China 81173320

The National Basic Research Program of China 2015CB554504

Title: Expression of TRPV1 regulated by STAT5 in hippocampus

Authors: ***L. HUANG**, J. LIU, Y. WANG, H.-Y. YIN, C.-S. ZHANG, S.-G. YU, Y. TANG; Sch. of Acupuncture, Chengdu Univ. of Traditional Chinese Med., Sichuan, China

Abstract: Transient receptor potential vanilloid 1 (TRPV1) channel has been found to be expressed in hippocampus and contributed to synaptic plasticity,neurotransmitter release, etc. Signal transducers and activators of transduction 5 (STAT5), a transcription factor, has demonstrated to get involved in neuroprotective and neurotrophic effects in hippocampus.However, whether the function of STAT5 would exert impact on TRPV1 was unclear. To answer this question, we employed TRPV1 knockout mice to test the expression of STAT5 in hippocampus and then generated STAT5 conditional knockout mice through STAT5 flox and Nestin-cre system to measure the expression of TRPV1 in hippocampus. Our results indicated that in TRPV1-deficient mice, the expression of STAT5 did not show any significant changes while the expression of TRPV1 was raised in the absence of STAT5. Therefore, the current data suggests that the expression of TRPV1 in hippocampus is regulated by STAT5.

Disclosures: **L. Huang:** None. **J. Liu:** None. **Y. Wang:** None. **H. Yin:** None. **C. Zhang:** None. **S. Yu:** None. **Y. Tang:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 573.01/B56

Topic: B.08. Synaptic Plasticity

Support: NIH MERIT Award R37 MH057068

NIH Grant R01 MH53576

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The Lightfighter Trust

Title: Compensation for PKMζ function in spatial long-term memory in mutant mice

Authors: *C. HSIEH[1], P. TSOKAS[1,2], T. C. SACKTOR[1,3,2];
[1]Dept of Physiol. and Pharmacol., [2]Dept. of Anesthesiol., [3]Dept. of Neurol., SUNY Downstate Med. Ctr., Brooklyn, NY

Abstract: PKMζ, a brain-specific, constitutively active, atypical protein kinase C isoform has been proposed to be crucial for the maintenance of late-LTP (L-LTP) and spatial long-term memory (LTM). Recent results from PKCζ/PKMζ null mice, however, have questioned this hypothesis. Using a pharmacogenetic approach (see Tsokas et al., SfN 2015), we showed that in PKMζ-null mice L-LTP is mediated by compensatory mechanisms, whereas in wild-type mice L-LTP is mediated by PKMζ. Here we show that similar to L-LTP, in PKMζ-null mice spatial LTM is mediated by compensatory mechanisms, and spatial LTM in wild-type mice by PKMζ. To determine the role of PKMζ in spatial LTM, we examined active place avoidance, a conditioned spatial behavior that is both rapidly learned and hippocampus-dependent. We found that 24 hr after active place avoidance training PKMζ protein levels are elevated in the dorsal hippocampus of adult mice. This suggests that similar to L-LTP, spatial LTM requires de novo synthesis of PKMζ. Using implanted guided cannulae targeting the dorsal hippocampus, we injected bilaterally the same PKMζ-antisense oligodeoxynucleotide (AS-ODN) construct we used in Tsokas et al., (SfN 2015) to block LTP in wild-type mice, or its scrambled control (SCR-ODN). We injected 2 nmol/µl ODN in PBS (0.5 µl/side) 20 min before each of three 30-min training sessions, spaced 2 hours apart. Antisense oligodeoxynucleotides injected in this manner into the hippocampus last at least 2 hours. We found that the PKMζ-antisense disrupts 1-day LTM in wild-type mice, but not in the PKMζ-null. Thus, spatial LTM, like L-LTP, is mediated by compensatory mechanisms in mutant mice, and by PKMζ in wild-type mice.

Disclosures: C. Hsieh: None. **P. Tsokas:** None. **T.C. Sacktor:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 573.02/B57

Topic: B.08. Synaptic Plasticity

Support: DGIST R&D Program of the Ministry of Science, ICT&Future Planning (15-BD-06)

Title: miR-204 regulates surface expression of NMDA receptor through repressing EphB2 in mouse hippocampal neurons

Authors: *K. KIM, H. NAM, C. DANKA, K. KIM;
DGIST, Daegu, Korea, Republic of

Abstract: In order to gain an insight into how changes in miRNAs expression affect hippocampal function during aging, we performed small RNA profiling at seven different life stages of mouse hippocampus. Bioinformatical analysis of these small RNAs indicate that 55 miRNAs are differentially expressed showing more than two fold change between young (2M) and old (18M) mouse hippocampus and that their potential target mRNAs are important components in neuronal regulation pathways including axon guidance. Here we report that Eph-ephrin signaling pathway is significantly downregulated in aged hippocampus. mRNA levels of ephrin signaling molecule EphB2 decreased and its inhibitory molecule RhoA increased between young (2M) and old (18M) stages. We found that miR-204 is upregulated in old hippocampus and targets EphB2 in a dose dependent manner in neurons. Importantly, miR-204 regulates NMDA receptor trafficking by specifically inhibiting surface expression of NR1 subunit in neurons whereas inhibition of miR-204 promotes its surface expression. These findings indicate miR-204 is an important regulator of synaptic plasticity and NMDAR function that have association with age dependent decline in cognition.

Disclosures: **K. Kim:** None. **H. Nam:** None. **C. Danka:** None. **K. Kim:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 573.03/B58

Topic: B.08. Synaptic Plasticity

Title: An NMDA receptor S1166A KI mouse exhibits impaired synaptic plasticity at CA1 synapses

Authors: *M. W. PORCH[1,2], J.-Y. HWANG[2], R. S. ZUKIN[2], A. E. CHÁVEZ[2];
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Abstract: NMDARs are glutamate-gated ion channels and are enriched at excitatory synapses, where they are strategically positioned to play a crucial role in regulation of synaptic function. A unique feature of NMDARs is their high permeability to Ca2+. Ca2+ influx through NMDARs is essential for synaptogenesis, plasticity of neural circuitry, and higher cognitive functions, such as learning and memory. Emerging evidence reveals that PKA signaling represents a fundamental mechanism by which NMDAR-mediated Ca2+ influx is modulated in neurons. Direct activation of PKA promotes NMDAR Ca2+ permeability, Ca2+ signaling in dendritic spines, and induction of LTP at Schaffer collateral to CA1 pyramidal cell synapses. Consistent with this, extracellular signals that modulate cAMP bidirectionally regulate Ca2+ permeation through NMDARs and Ca2+ transients in spines in a PKA-dependent manner. We recently identified phosphorylation of GluN2B at Ser1166 to be the molecular target of PKA relevant to NMDAR Ca2+ permeability. Whereas the impact of PKA induced phosphorylation of Ser1166 on NMDAR Ca2+ permeability is well-established, its impact on NMDAR-dependent synaptic plasticity is unclear. To address this issue, we generated a mouse with a S1166A mutation knocked-in by means of the CRISPR method. These mice developed and bred normally and did not exhibit any gross morphological phenotypes. We first assessed basal synaptic transmission by monitoring the input/output relation at Schaffer collateral to CA1 synapses. The S1166A mutation does not alter basal transmission relative to wild-type controls. Next we investigated presynaptic function by means of paired-pulse facilitation at CA1 synapses. Paired-pulse facilitation was not altered in these mice relative to wild-type controls. We next examined the impact of the S1166A mutation on synaptic plasticity at CA1 synapses. Whereas theta-burst stimulation LTP was greatly diminished, high frequency stimulation at CA1 synapses exhibited little or no change relative to that of wild-type mice. These findings indicate a novel and previously unappreciated role for PKA phosphorylation of the NMDA receptor subunit GluN2B at Ser1166 on specific forms of synaptic plasticity at hippocampal synapses.

Disclosures: **M.W. Porch:** None. **J. Hwang:** None. **R.S. Zukin:** None. **A.E. Chávez:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: B.08. Synaptic Plasticity

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Dicyt-USACH 021343MM

Title: Methylphenidate enhance long-term potentiation in CA3-CA1 hippocampal synapse involving insertion of functional AMPA receptors

Authors: G. UGARTE, C. CARVALLO, C. ROZAS, D. CONTRERAS, R. FARÍAS, R. DELGADO, M. ZEISE, *B. E. MORALES;
Univ. of Santiago, Santiago, Chile

Abstract: Methylphenidate (MPH, Ritalin©) is used in the treatment of Attention Deficit Hyperactivity Disorder and recently as abuse drug. Although it is known that MPH increases the TBS-dependent Long Term Potentiation (LTP) in hippocampus, the cellular and molecular mechanisms involved in this process are unknown. Using electrophysiological approaches and Western blot analysis we investigated the effect of MPH on LTP in hippocampal slices obtained from young rats (3-4 weeks). LTP in CA3-CA1 were induced by applying theta burst stimulation (TBS, 5 trains, 100 Hz). Superfusion with MPH during 20 min, significantly increased the magnitude of hippocampal LTP in a dose-dependent manner with a EC50 of 73.44 ± 6.32 nM. Paired-pulse facilitation curves remained unchanged after perfusion with MPH, suggesting that the effect of MPH does not involve presynaptic components. The increase induced by MPH was inhibited by the β-adrenergic blocker timolol (5 μM), from 194.3±5.8% to 152.7±1.7% (n=4,4; $p<0.01$). We also evaluated the dopaminergic contribution in the effect of MPH. Interestingly, LTP increase was also inhibited by 5 μM of SCH23390, a D1/D5 receptors blocker, from 193.1 ± 8.0 % to 144.4 ± 3.2% (n = 5,7; $p < 0.001$). The inhibition of PKA by PKI suppresses the MPH-dependent enhancement of LTP, suggesting that downstream activation of cAMP/PKA-dependent cascade. To determine whether the facilitation of LTP induced by MPH involves the insertion of new AMPA receptors in the postsynaptic membrane, CA1 areas from hippocampal slices used in LTP experiments were collected and Western blot analysis for phosphosphorylations in GluR1 was performed. CA1 areas from slices showing an enhanced LTP after perfusion with 5 μM MPH exhibited a significant increase of 28 ± 6 % in

phosphorylation of Ser845 residues (n=9,9; $p<0.05$) compared to slices with TBS-dependent LTP without MPH. No significant change in the phosphorylation state of Ser831 was observed (n=9,9; $p > 0.05$). In addition, the phosphorylation of Ser845 induced by MPH was inhibited by SCH23390 (n=4,4; $p > 0.05$). Cross-linking experiments for membrane-associated AMPA receptors are being performed to confirm these results. Finally, using whole cell recordings in pyramidal cells of CA1 we found a significant increase in short term plasticity of AMPA-dependent postsynaptic currents after perfusion with 5 μM MPH. No changes were observed in NMDA-dependent currents. Altogether, these results suggest that the increase of CA3-CA1 LTP induced by MPH involve β-adrenergic and dopaminergic components promoting the insertion of new AMPA receptors in the postsynaptic membrane through phosphorylation of Ser845 residues in GluR1 subunits.

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Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 573.05/B60

Topic: B.08. Synaptic Plasticity

Title: Regulation of NMDA receptor 2B expression in layer IV barrel cortex by CaMKII

Authors: *S. KO, S. CHUNG;
Yonsei Univ., Seoul, Korea, Republic of

Abstract: Regulation of NMDA receptor 2B expression in layer IV barrel cortex by CaMKII
Glutamate (Glutamic acid) is an essential excitatory neurotransmitter in mammalian central nervous system and acts on both metabotropic and ionotropic glutamate receptors (iGluRs). The iGluRs are divided into three groups according to their agonist selectivity: NMDA, AMPA and kinate receptors. Ionotropic glutamate receptors are ligand-gated ion channels that mediate the major excitatory neurotransmission. NMDA receptors are widely expressed in the central nervous system that play key role in excitatory synaptic transmission. Among the NMDA receptor subunits, NR2B is highly expressed in the hippocampus and cerebral cortex and plays important roles in synaptic plasticity, learning and memory. NR2B expression peaks in the hippocampus and cortex during the third postnatal week and then declines to moderate/low adult levels. However, the regulatory mechanisms of NR2B expression in developmental stage in layer IV barrel cortex are not clear. Recent study showed that in developmental stages, NMDA

receptor expression in barrel cortex is control the process of thalamocortical afferent innervation, segregation, and plasticity. In addition, NR2B have been reported to interact with several proteins such as Ca^{2+}/calmodulin-dependent kinase II (CaMKII), small GTPases, Homer. In the present study, we find that in adult whisker nerve injury model rat, NR2B protein expression levels were increased like NR1A protein expression and it regulated by CaMKII activities. These finding support the better understanding the regulatory mechanism of NR2B protein in the layer IV barrel cortex.

Disclosures: S. Ko: None. **S. Chung:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

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Topic: B.08. Synaptic Plasticity

Support: ERC Grant RQ8898

WCU Grant

Title: Stimulus parameters determine the role of PKA, protein synthesis and CP-AMPARs in LTP at hippocampal CA1 synapses

Authors: *P. PARK[1,2], B.-K. KAANG[2], G. L. COLLINGRIDGE[1,2,3];
[1]Univ. of Bristol, Bristol, United Kingdom; [2]Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Univ. of Toronto, Toronto, ON, Canada

Abstract: Long-term potentiation (LTP) has been considered to be the best cellular correlate of learning and memory. In the hippocampal CA1 synapses, two different forms of LTP have been reported in terms of underlying cellular mechanisms, as early LTP (E-LTP) and late LTP (L-LTP). L-LTP requires the process of PKA and protein synthesis, and is maintained as long as experiments are continued, while E-LTP only lasts for a few hours. However, this LTP dichotomy has been controversial because of its vague criteria and inconsistent results. Our previous report (Park et al., 2014) suggested that long-lasting LTP exists as two distinct forms following synaptic mechanisms and the requirement of certain stimulus parameters; which we referred to as LTPb and LTPc (sparing LTPa to presynaptic short-term potentiation). LTPb was induced by a single high-frequency stimulation (HFS) or compressed multiple HFSs (e.g. 3 HFS at 10 sec interval), and did not require the process of PKA and protein synthesis. On the other

hand, LTPc was induced when the same number of HFSs given at longer interval (e.g. 3 HFS at 10 min interval), and mediated by PKA and protein synthesis dependent mechanism. In this study, we used simultaneous field and patch electrophysiology to further understand the mechanism of these two forms of LTP. Theta-burst stimulation (TBS) was used, rather than HFS, for its induction protocol (we couldn't find any differential effect of TBS and HFS on LTPb/LTPc mechanism), and various drug combinations were applied to specifically antagonise the molecules of interest in the acute slices. Here, we show a line of evidence suggesting that calcium-permeable AMPA receptors (CP-AMPARs) are transiently recruited on the synaptic surface by LTPc induction, and are required for its expression. LTPc, but not LTPb, was time-dependently sensitive to three different types of CP-AMPAR blockers, philanthotoxin 433 (5 - 10 μM), NASPM (30 μM) and IEM 1460 (30 μM) in the extracellular recording. This transient CP-AMPAR expression was also confirmed by AMPAR inward-rectification via whole cell recording. Moreover, a weak TBS-induced LTP was significantly enhanced in the presence of rolipram (100 nM, PDE4 inhibitor) via a PKA dependent mechanism. This effect was completely reversed by IEM 1460 (30 μM), suggesting PKA-dependent LTP is mediated by CP-AMPARs. In conclusion, LTP can be maintained for a long time via two disparate cellular mechanisms whether or not PKA, protein synthesis and CP-AMPARs are involved. This is determined by the time interval afforded between multiple LTP inductions. And importantly, PKA-dependent LTP in our study is mediated by CP-AMPARs.

Disclosures: P. Park: None. **B. Kaang:** None. **G.L. Collingridge:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

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Program#/Poster#: 573.07/B62

Topic: B.08. Synaptic Plasticity

Title: Modeling the signaling mode of calcium influx through L-type calcium channels to the nucleus

Authors: *X. LI[1], W. HOLMES[2];
[1]Ohio Univ., Athens, OH; [2]Ohio, Athens, OH

Abstract: Calcium signals are important for learning and memory at the cellular level. Calcium can enter the cell body from L-type channels, triggering a series of downstream cascades, including the phosphorylation of CREB in the nucleus. How calcium carries out the journey from the membrane to the nucleus is debated. One line of studies has suggested that calcium ions

are taken to the nucleus by carrier proteins including calmodulin (CaM) and CaMKII gathered around the nanodomain of L-channels. This is known as a local signaling mode. Other studies have indicated that Ca2+ influx increases the overall bulk concentration in the cytosol and then diffuses into the nucleus. This is known as a global signaling mode. To test the signaling modes, we built a biophysically realistic computational model. A chunk of the cell body was modeled in a pyramid shape, with the apex toward the nucleus and the base as the membrane. The model includes three compartments: the shell, the cytosol and the nucleus. Molecule positions and reactions were tracked in these compartments. Molecules included in the model are Ca2+, CaM, βCaMKII and γCaMKII. The signaling cascade is modeled as follows: Ca2+ is taken up by CaM and together is bound by CaMKII. βCaMKII facilitates the phosphorylation of γCaMKII. γCamKII then carries the Ca2+/CaM to the nucleus. The reaction and diffusion process was modeled stochastically with Smoldyn. The reaction network was generated using BioNetGen. We examined the distribution of Ca2+ in terms of free Ca2+ ions or Ca2+ bound to CaM or CaMKII under different stimulation patterns and distributions of CaM. At early times the majority of Ca2+ in the shell and cytosol is bound to either CaM or CaMKII rather than staying free. This is consistent with the local signaling mode. The proportion of Ca2+ being bound varies with the Ca2+ input pattern. A steady influx of Ca2+ allows more Ca2+ bound to CaM but less bound to CaMKII. In contrast, burst influx (3 Ca2+ spikes) allows more Ca2+ to be bound to CaMKII but less to CaM. The distribution of CaM also plays a role. Compared with the uniform distribution of CaM in the cytosol and the shell, a nonuniform distribution of CaM (1 mM in the shell and 10 uM in the cytosol) leads to less Ca2+ bound to CaMKII and more bound to CaM. In summary, the preliminary data generated by the model suggests that in a short time scale the majority of Ca2+ binds to the carrier proteins (CaMs and CaMKIIs) before entering the nucleus and therefore supports a local signaling mode. However, it is unknown whether the global signaling mode may coexist in a longer time scale. Our future work will include the downstream cascades in the nucleus and examine the long term effect of Ca2+ signaling.

Disclosures: **X. Li:** None. **W. Holmes:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 573.08/B63

Topic: B.08. Synaptic Plasticity

Support: Bergen Research Foundation

Title: Exploring Arc protein complexes in SH-SY5Y neuroblastoma cells

Authors: O. NIKOLAIENKO, *C. R. BRAMHAM;
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Abstract: The immediate early gene ARC (also known as ARG3.1) encodes a synaptic protein that functions in multiple forms of neuronal plasticity (long-term potentiation, long-term depression, and homeostatic plasticity). Its expression is tightly controlled by a unique combination of molecular mechanisms - fast activity-induced mRNA synthesis by poised RNA polymerase followed by dendritic transport, translation, nonsense-mediated RNA decay and rapid degradation of the protein. Arc multiple functions within distinct subcellular compartments suggests the existence of different protein complexes, which composition is potentially regulated by Arc post-translational modifications (PTMs). To date, little information on Arc PTMs and their functional significance is available, and it is still not known if they influence the Arc interaction interface and trigger/block the binding to other proteins. To address this question we developed a procedure for two-step affinity purification of Arc protein complexes from SH-SY5Y neuroblastoma cells. Followed by tandem mass spectrometry it allowed the identification of previously unknown Arc protein partners and a number of new Arc PTMs. Our results show that Arc is extensively regulated by phosphorylation in neuroblastoma cells. Further experiments are needed to determine the effect of these modifications.

Disclosures: O. Nikolaienko: None. **C.R. Bramham:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 573.09/B64

Topic: B.08. Synaptic Plasticity

Support: National Medical Research Council Collaborative Research Grant (NMRC-CBRG-0041/2013)

NUS Research Scholarship to M.S.S

Ministry of Education Academic Research Funding (MOE AcRF- Tier 1 - T1-2012

Title: Dopaminergic signalling regulates synaptic cooperation and competition of associative plasticity through differential activation of extracellular signal-regulated kinases (ERK1/2)

Authors: *M. S. SHETTY[1,2], S. GOPINADHAN[1,2], S. SAJIKUMAR[1,2];
[1]Dept. of Physiology, Yong Loo Lin Sch. of Med., Natl. Univ. of Singapore, Singapore, Singapore; [2]Neurobiology/Aging Program, Level-4, Life Sci. Inst. (LSI), Singapore, Singapore

Abstract: Role of dopaminergic mechanisms in hippocampal long-term plasticity and memory is well established. Altered dopaminergic signalling and modulation in the hippocampal circuits has been implicated in the pathophysiology of many neuropsychiatric disorders, and also in the age-associated memory deficits. Consequently, administration of dopamine agonists has been reported in many cases to alleviate or restore the alterations. Though dose-dependent differences in the dopamine-mediated mechanisms are reported in certain brain regions, similar effects in hippocampus have not been investigated. Here, using acute hippocampal slices from rats, we have performed long-term plasticity experiments under the conceptual framework of synaptic tagging and capture hypothesis. Our results demonstrate that D1/D5-receptor-mediated potentiation at the CA3-CA1 Schaffer collateral synapses differentially regulates synaptic co-operation and competition to establish long-term plasticity in a dose-dependent manner. Further investigating the molecular players involved, we reveal an important role for extracellular signal-regulated kinases-1 and 2 (ERK1/2) as signal integrators and dose-sensors. The concentration-dependent effects of the modulatory transmitter, as demonstrated for dopaminergic signalling in the present study, might offer additional computational power by fine tuning synaptic co-operation and competition for establishing long-term associative memory in neural networks. Our study provides important insights into how the changes in the extracellular dopamine concentrations influence the ongoing information processing and affect the encoding and maintenance of memories. These findings are significant in the context of learning-induced and drug-induced changes in hippocampal dopamine.

Disclosures: **M.S. Shetty:** None. **S. Gopinadhan:** None. **S. Sajikumar:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 573.10/B65

Topic: B.08. Synaptic Plasticity

Support: PAPIIT IN212013

CONACYT 367853

Title: CaMKII is required for long-term memory of conditioned taste aversion and its modulation of neocortical LTP

Authors: *Y. JUAREZ MUÑOZ, M. L. ESCOBAR;
Div. de Estudios de Posgrado, Facultad De Psicologia, UNAM, Distrito Federal, Mexico

Abstract: A central question in the field of cognitive neuroscience refers to the maintenance of long-term memory. Among the proposed molecules required for memory persistence, calcium/calmodulin-dependent protein kinase II (CaMKII) is a suitable candidate since it has the ability to remain active, through intersubunit autophosphorylation, even when the initial calcium stimulus has decayed. Previous work from our laboratory showed that training in conditioned taste aversion (CTA), an insular cortex (IC) dependent task, prevents the induction of long-term potentiation (LTP) in the basolateral amygdaloid nucleus (Bla)-IC projection, producing a metaplastic effect, i.e. a change in the ability to induce subsequent synaptic plasticity. In order to explore the molecular mechanisms that underlie memory persistence, we evaluated the effect of local IC microinfusion of a selective inhibitor of CaMKII in the maintenance of CTA memory as well as in the metaplastic effect produced by CTA over the subsequent induction of LTP. Our results show that CaMKII is required for CTA long-term memory and modifies the ability for subsequent induction of synaptic plasticity in the Bla-IC pathway. These results indicate that CaMKII is a central key component for long-term memory storage of aversive tasks as well as for the homeostatic plasticity processing. Supported by PAPIIT IN212013

Disclosures: Y. Juarez Muñoz: None. **M.L. Escobar:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 573.11/B66

Topic: B.08. Synaptic Plasticity

Support: Max Planck Florida Institute

Title: The role of autophosphorylation at Thr286 of CaMKII in single dendritic spines during long-term potentiation

Authors: *J.-Y. CHANG[1,2], P. PARRA-BUENO[1], R. YASUDA[1];
[1]Max Planck Florida Inst., Jupiter, FL; [2]Duke Univ., Durham, NC

Abstract: Ca^{2+}/CaM -dependent protein kinase II (CaMKII) has a central role in long-term potentiation (LTP), which is believed to be a cellular form of learning and memory. Despite the great number of the signaling molecules that are required for LTP, little is known about how the initial NMDA-receptor mediated Ca^{2+} transients transduces into the long-lasting modification of cellular process in supporting LTP. The initial influx of Ca^{2+} relays the extracellular signaling to LTP by activating calmodulin (Ca^{2+}/CaM), which in turn activates several downstream signaling molecules including CaMKII. Activation of CaMKII depends both on the binding of Ca^{2+}/CaM, and on the autophosphorylation at Thr286. Phosphorylation at T286 generates Ca^{2+}/CaM independent (autonomous) activity of CaMKII, and this prolonged activity is required for LTP, spatial learning and memory. However, it remains uncertain about the temporal requirement of CaMKII T286 phosphorylation during LTP. Here, by using CaMKII FRET sensor (camuiα) combined with ultra-fast temporal resolution (8Hz) of two-photon fluorescence lifetime imaging microscopy (FLIM), we showed that 1) CaMKII functions as a biochemical integrator of multiple Ca^{2+} pulses during LTP induction and autophosphorylation at T286 is required to efficiently integrate Ca^{2+} pulses. 2) During LTP induction, Ca^{2+}/CaM binds persistently to a fraction of activated CaMKII and autophosphorylation at T286 is required for the persistent binding of Ca^{2+}/CaM. 3) Phosphorylation at T286 is only required during LTP induction. Together, these findings elucidate the critical role of CaMKII T286 phosphorylation during the initial Ca^{2+} signaling steps in LTP.

Disclosures: J. Chang: None. **P. Parra-Bueno:** None. **R. Yasuda:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 573.12/B67

Topic: B.08. Synaptic Plasticity

Title: Hebbian long-term potentiation in feed-forward hippocampal interneurons

Authors: *M. MERCIER, D. KULLMANN;
Inst. of Neurol., Univ. Col. London, London, United Kingdom

Abstract: Long-term potentiation (LTP) of excitatory transmission in hippocampal principal cells is thought to play an important role in memory encoding. Within area CA1, LTP in pyramidal cells depends on Ca^{2+} influx through postsynaptic *N*-methyl-D-aspartate (NMDA) receptors, and the subsequent phosphorylation of the α isoform of Ca^{2+}/calmodulin-dependent kinase type II (αCaMKII). Interestingly, a similar form of Hebbian LTP has been described in

CA1 feed-forward inhibitory interneurons, located in stratum radiatum, which serves to maintain the temporal fidelity of synaptic integration in pyramidal cells[1]. Unlike pyramidal cell LTP, however, this form of plasticity is only observed in ~50% of interneurons, and depends on a non-α isoform of CaMKII[2]. The perforated-patch clamp technique is necessary to observe interneuron LTP, as whole-cell recordings have been found to induce rapid run-down of NMDA receptor-mediated signaling in these cells[1]. Alternatively, feed-forward interneuron LTP can also be detected indirectly using whole-cell recordings from pyramidal cells, where an increase in disynaptic inhibition can be seen. In order to evoke and record such disynaptic responses, acute mouse hippocampal slices were taken and whole-cell voltage clamp recordings made from CA1 pyramidal cells, located distant (>1 mm) from the stimulation site at the Schaffer collateral pathway; cells were held close to the reversal potential for glutamate receptors in order to selectively detect inhibitory postsynaptic currents (IPSCs). In line with previous work, a pairing protocol designed to induce Hebbian LTP in local stratum radiatum interneurons led to a persistent increase in disynaptic IPSC amplitude in pyramidal cells. This enhancement of inhibition was blocked by D-(-)-2-amino-5-phosphonopentanoic acid (AP5), importantly confirming its dependence on NMDA receptor signaling. Interestingly, the potentiation was only evident in mice aged P20 or older, suggesting that the expression of Hebbian LTP in feed-forward interneurons may be developmentally regulated. Further experiments employing the perforated-patch clamp technique will seek to corroborate these findings and further probe the signaling pathways and mechanisms involved in this relatively unknown form of hippocampal plasticity. Footnotes [1] Lamsa, K., Heeroma, J.H., Kullmann, D.M. (2005). *Nat. Neurosci.* **8**: 916-24 [2] Lamsa, K., Irvine, E.E., Giese, K.P., Kullmann, D.M. (2007). *J. Physiol.* **584**: 885-94

Disclosures: **M. Mercier:** None. **D. Kullmann:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 573.13/B68

Topic: B.08. Synaptic Plasticity

Support: GM058234

NS24067

MH071739

Simons Foundation

G Harold and Leila Y. Mathers Foundation

Burnett Family Foundation

Title: CaMK2G, an intellectual disability candidate gene, is critical for spatial learning by controlling activity-dependent BDNF synthesis in the hippocampus

Authors: *H. MA, S. SANCHEZ, I. KATS, B. SUUTARI, R. TSIEN;
Neurosci., New York Univ., New York, NY

Abstract: Intellectual disability (ID) is characterized by significant limitations in both intellectual functioning and adaptive behavior. We have identified γCaMKII, encoded by an ID candidate gene, as a Ca2+/CaM shuttle protein to support membrane signaling to nucleus for excitation-transcription (E-T) coupling. Interestingly, various players in this pathway (CaV1 channels, γCaMKII, βCaMKII, calcineurin and CaMKIV) are encoded by genes associated with several neuropsychiatric disorders including autism spectrum disorder, schizophrenia and major depression disorder. Since these disorders often share certain ID symptoms, it is intriguing that many of the associated genes also functionally converge on a common cellular pathway. To test whether there is a link between this pathway and ID as well as other neuronal disorders, we probed γCaMKII mediated E-T coupling and its consequences in mice lacking γCaMKII. The CaMK2G KO mice were normal in general health and basic behavior. No change in anxiety was found in open field test or elevated zero maze. However, in the marble bury test CaMK2G KO mice buried marbles fourfold more than their WT littermates, which suggests a repetitive perseverative behavior phenotype. In the forced swim test, a test developed for screening potential antidepressant drugs, CaMK2G KO mice showed a markedly increased immobility. Thus, in addition to having repetitive behavior often found in animal models of autism, CaMK2G KO mice also showed depression-like behavior. In people with ID, the intellectual functioning is often limited. To assess the learning ability of CaMK2G KO mice, spatial memory acquisition and retrieval were tested in Morris water maze (MWM). Strikingly, CaMK2G KO mice show limited learning to find a hidden platform, as well as inability to recall that location after platform removal. To further validate this, we tested mice in a radial arm maze, which invokes different motivations and motor systems. Consistent with our findings in MWM, CaMK2G KO mice also showed significantly impaired reference memory in radial arm maze. Since CREB-dependent gene expression is critical for neuronal plasticity, we asked whether activity-dependent gene expression and protein synthesis in γCaMKII KO mice are defective. No significant change was found for activity-related proteins such as receptors for GABA, NMDA and AMPA. However, BDNF, a CREB-targeted gene, increased more than 2 fold with MWM training, which was strikingly prevented in CaMK2G KO mice. Interestingly, the inhibition of BDNF expression was not caused by a prevention for MAPK pathway, suggesting a specific and critical role of γCaMKII-mediated E-T coupling in spatial learning.

Disclosures: **H. Ma:** None. **S. Sanchez:** None. **I. Kats:** None. **B. Suutari:** None. **R. Tsien:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 573.14/B69

Topic: B.08. Synaptic Plasticity

Support: R01MH077022

Title: Role and regulation of CRTC1 phosphorylation during activity-dependent synaptic plasticity

Authors: ***M. DESALVO**[1], T. CH'NG[2,3], A. VASHISHT[1], J. WOHLSCHLEGEL[1], K. MARTIN[1,4];
[1]UCLA Biol. Chem., UCLA, Los Angeles, CA; [2]Lee Kong Chian Sch. of Med., [3]Sch. of Biol. Sci., Nanyang Technological Univ., Singapore, Singapore; [4]Integrative Ctr. for Learning and Memory, UCLA Brain Res. Inst., Los Angeles, CA

Abstract: Previous studies have shown that CREB Regulated Transcriptional Co-activator 1 (CRTC1) plays a critical role in learning and memory by regulating gene expression in neurons. Our lab has shown that CRTC1 localizes at synapses and undergoes activity-regulated translocation to the nucleus where it interacts with CREB and other transcription factors to trigger changes important for the late phase of long-term potentiation (L-LTP). CRTC1 is heavily phosphorylated and its phosphorylation state changes dramatically upon stimulation. We have identified 50 phosphorylation sites in CRTC1 and are currently characterizing key sites that could be important not only in synapse to nuclear transport, but also for CRTC1's transcriptional role in the nucleus. We have created several phospho-incompetent mutants and are currently testing their effects in cultured cortical neurons. We hypothesize that different stimulation conditions cause distinct phosphorylation changes that inform both the trafficking and transcriptional role of CRTC1. We are using affinity purification and mass spectrometry to identify phosphorylation sites that are specifically affected during activity. To look at the effects of these mutants on transcription, we are using chromatin immunoprecipitation (ChIP) sequencing to identify genes that are differentially transcribed. De-coding the role of phosphorylation in the synapse to nuclear transport and transcriptional activity of CRTC1 is crucial to understand the complex regulation of plasticity in neurons.

Disclosures: **M. Desalvo:** None. **T. Ch'ng:** None. **A. Vashisht:** None. **J. Wohlschlegel:** None. **K. Martin:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 573.15/B70

Topic: B.08. Synaptic Plasticity

Support: NIH MERIT Award R37 MH057068

R01 MH53576

R01 DA034970

Lightfighter Trust

Title: Compensation for PKMζ function in late-LTP in mutant mice

Authors: *P. TSOKAS[1], T. C. SACKTOR[2,3,4];
[1]Furchgott Ctr. for Neural & Behav. Sci., Physiol. & Pharmacol., Anesthesiol., SUNY Downstate Med. Center, Brooklyn, NY, Brooklyn, NY; [2]Furchgott Ctr. for Neural & Behav. Sci., Physiol. & Pharmacol., SUNY Downstate Med. Ctr., Brooklyn, NY, NY; [3]Dept. of Neurol., [4]Dept. of Anesthesiol., SUNY Downstate Med. Ctr., Brooklyn, NY

Abstract: PKMζ is a persistently active kinase proposed to mediate late-LTP (L-LTP) and long-term memory. But these functions seem unaffected in PKMζ-null mice. We devised a pharmacogenetic approach to test whether compensatory mechanisms mediate LTP in PKMζ-null mice. PKMζ is generated by a dedicated PKMζ mRNA that encodes an independent PKCζ catalytic domain without a regulatory domain. Under basal conditions in neurons the PKMζ mRNA is translationally repressed, but LTP induction derepresses it, resulting in increased do novo PKMζ synthesis. Thus, if PKMζ-null mice produce L-LTP by a compensatory mechanism--and wild-type mice by synthesis of PKMζ--then PKMζ-antisense oligodeoxynucleotides (AS-ODN) will have no effect on LTP in the PKMζ-nulls, but block L-LTP in the wild-types. We first confirmed that bath application of AS-ODN to hippocampal slices selectively blocks de novo synthesis of PKMζ in wild-type mice during LTP, without affecting other activity-dependent gene products. We applied AS-ODN complementary to the PKMζ mRNA translation start site or a scrambled control oligodeoxynucleotides (SCR-ODN) to hippocampal slices for 2 hours prior to afferent tetanic stimulation of Schaeffer collateral/commissural-CA1 synapses.

Thirty min after tetanization, we measured protein levels in CA1 when the tetanic stimulation increases the expression of multiple activity-dependent gene products. We found that the PKMζ-antisense blocks the activity-dependent formation of PKMζ, but not that of the other atypical PKC, PKCι/λ, or the translation factor eEF1A. We then tested the effect of the drug on L-LTP in wild-type mice and PKMζ-null mice. Consistent with previous results, we found that L-LTP appears similar in PKMζ-null and wild-type mice. But the underlying molecular mechanisms for L-LTP in the two genotypes are different--the PKMζ AS-ODN has no effect on LTP in the PKMζ-null-mutant without the target PKMζ mRNA, but blocks L-LTP in wild-type mice. Thus, PKMζ-null mice mediate L-LTP by compensatory mechanisms, and wild-type mice by PKMζ.

Disclosures: P. Tsokas: None. **T.C. Sacktor:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 573.16/B71

Topic: B.08. Synaptic Plasticity

Support: NIH Grant NS081978

NIH Grant NS066583

Title: Proteasome inhibition lowers the threshold for CREB phosphorylation and L-LTP induction

Authors: *S. V. BACH, A. VASHISHT, J. W. MORGAN, T. K. SMITH, A. N. HEGDE; Wake Forest Univ., Winston Salem, NC

Abstract: The ubiquitin-proteasome pathway (UPP) plays a role in both induction and maintenance of the late phase of long-term potentiation (L-LTP). Previously we showed that inhibition of the proteasome with a specific and irreversible inhibitor, clasto-lactacystin β-lactone, enhances the induction of L-LTP but blocks its maintenance in the CA1 region of the murine hippocampus. We showed that proteasome inhibition enhances L-LTP induction by stabilizing the translational activators and inhibits maintenance of L-LTP by stabilizing the translational as well as transcriptional repressors. In this study, we examined whether proteasome inhibition affects the phosphorylation of the cAMP response element-binding protein (CREB), a key step in the induction of gene expression in L-LTP. Previous work showed that three- or four-train of high frequency (100Hz) tetanization results in the upregulation of phospho-CREB

(pCREB) and the induction of L-LTP. To investigate the effects of proteasome inhibition on signaling leading to the phosphorylation of CREB we used a subthreshold L-LTP induction protocol of two-train stimulation with 100Hz, fixed hippocampal slices 1 min after the treatment, stained slices with an anti-pCREB (Ser-133) antibody and imaged using a confocal microscope. We found that the two-train stimulation protocol alone is insufficient to upregulate pCREB levels. In combination with β-lactone treatment, however, pCREB levels were significantly upregulated compared to untreated slices. Treatment of slices with β-lactone alone did not change pCREB levels as compared to untreated controls. We hypothesized that proteasome inhibition lowers the threshold for L-LTP induction via enhanced kinase activity. Therefore, we examined the role of proteasome inhibition on the activity of several known kinases that contribute to CREB phosphorylation in L-LTP. The application of specific inhibitors for protein kinase A, protein kinase G, and MAP kinase, in combination with β-lactone, blocked the proteasome inhibition-mediated enhancement of pCREB after the two-train tetanization protocol. These findings suggest that proteasome inhibition reduces the threshold for phosphorylation of CREB and L-LTP induction by enhancing general kinase activity. In combination with our previous findings that proteasome inhibition blocks proteolytic degradation of translational activators, it is possible that β-lactone treatment augments local translation of kinases (or of some other factor that positively affects kinase signaling) at stimulated synapses to promote cytoplasm-to-nucleus signaling and to enhance the induction of L-LTP.

Disclosures: **S.V. Bach:** None. **A. Vashisht:** None. **J.W. Morgan:** None. **T.K. Smith:** None. **A.N. Hegde:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 573.17/B72

Topic: B.08. Synaptic Plasticity

Support: NIMH Grant MH101703

NINDS Grant NS045260

Title: Abnormal mTOR signaling contributes to Ube3A deficiency-induced impairment in hippocampal synaptic plasticity and hippocampus-dependent memory

Authors: ***J. SUN**, Y. LIU, J. TRAN, P. O'NEAL, X. HAO, M. BAUDRY, X. BI;
Western Univ. of Hlth. Sci., Pomona, CA

Abstract: Angelman syndrome (AS) is a neurogenetic disorder caused by deficiency of maternally expressed UBE3A. Previous research has shown that both long-term potentiation (LTP) and learning and memory are impaired in AS mice. We previously reported that semi-chronic rapamycin treatment not only improved motor performance but also normalized mTORC1 and mTORC2 signaling in the cerebellum of AS mice. We showed that enhanced mTORC1 activation, due to the release of TSC2-imposed inhibition, was responsible for mTORC2 inhibition. We report here that a similar abnormal mTORC1 and mTORC2 signaling also exists in hippocampus of AS mice. We found that TSC2 inhibition was associated with increased mTORC1 activity as evidenced by increased S6K1 and S6 phosphorylation but decreased mTORC2 activity with reduced PKCα levels. mTORC2 inhibition was linked to S6K1-mediated inhibitory phosphorylation of its regulator, rictor. Immunostaining results confirmed that phosphorylation of S6K1 was increased while that of AKT was decreased in hippocampal CA1 region of AS mice. Semi-chronic treatment of AS mice with rapamycin normalized mTORC1 and mTORC2 signaling. These results support the notion that overactivation of mTORC1 as a consequence of TSC2 inhibition, suppresses mTORC2 via S6K1-mediated rictor phosphorylation. Furthermore, both rapamycin and the S6K1 inhibitor PF4708671 normalized LTP in hippocampal CA1 region in AS mice. More importantly, Ube3A deficiency-induced increase in Arc expression was markedly reduced by treatment with both rapamycin and PF4708671 in CA1 dendritic field of hippocampal slices. These results indicate a critical role for mTOR signaling pathway in regulating dendritic Arc protein synthesis in hippocampus. Finally, rapamycin treatment also improved dendritic spine morphology of CA1 pyramidal neurons and contextual memory in a fear-conditioning paradigm in AS mice, possibly through suppressing mTORC1-dependent dendritic Arc synthesis and increasing mTORC2-mediated regulation of synaptic cytoskeletal elements. Collectively, our results indicate that abnormal mTOR signaling may contribute to synaptic plasticity and learning and memory impairments in AS mice.

Disclosures: **J. Sun:** None. **Y. Liu:** None. **J. Tran:** None. **P. O'Neal:** None. **X. Hao:** None. **M. Baudry:** None. **X. Bi:** None.

Poster

573. Long-Term Potentiation Signaling Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 573.18/B73

Topic: B.08. Synaptic Plasticity

Support: NMRC

Title: An Arc-regulating chromatin modifying complex controls neuronal activity-dependent gene expression

Authors: *N. E. OEY, H. LEUNG, H. M. A. VANDONGEN, A. M. J. VANDONGEN; Duke-Nus Grad. Med. Sch., Singapore, Singapore

Abstract: Long-term memory formation is highly complex and likely requires the dynamic regulation of hundreds of neuronal activity-dependent genes. We have recently characterized a nuclear epigenetic complex that regulates the activity-dependent transcription of Arc, an immediate early gene that is important for memory consolidation1. This dual-function chromatin-modifying complex contains the X-linked Mental Retardation histone demethylase PHF8 and the Alzheimer's Disease-associated histone acetyltransferase TIP60, which act to modify chromatin at the H3K9S10P locus, enabling rapid activity-dependent gene transcription. While the transcriptional regulation is important for neuroplasticity, it is ultimately the expression of downstream effector genes that initiate the cascade of events leading to more permanent changes at the level of neuronal proteins. To demonstrate this, we developed a novel proteome-wide mass spectrometric quantitative assay to show that the expression of hundreds of neuroplasticity-related proteins change dramatically in response to neural network activity. However, inhibiting the function of the Arc-regulating epigenetic complex using either RNA interference or transfection of enzymatically inactive PHF8 causes massive downregulation of Arc and the activity-dependent proteome. These results suggest that the chromatin-modifying complex containing PHF8 may be important for the expression of many neuronal activity-dependent genes.

Disclosures: N.E. Oey: None. **H. Leung:** None. **H.M.A. VanDongen:** None. **A.M.J. VanDongen:** None.

Poster

574. Homeostatic Plasticity II

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 574.01/B74

Topic: B.08. Synaptic Plasticity

Support: Georgetown Howard Hughes University Grant

NIH/NINDS Grant NS080462

Title: Kappa opioid receptor signaling in hippocampal gain control and temporal lobe epilepsy

Authors: *R. L. DUNN[1], B. N. QUEENAN[2], P. A. FORCELLI[1], D. T. S. PAK[1]; [1]Pharmacology/Physiology, Georgetown Univ., Washington, DC; [2]Neurosci., Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Neurons form signaling networks via synapses, sites of contact between neurons. The strength of synapses can be modulated to encode information (Hebb 1949; Magee & Johnston 1997 Science) or stabilize networks (Turrigiano 1998 Nature; O'Brien 1998 Neuron; Turrigiano 2008). In cases of chronic neuronal hyperactivity, there is broad compensatory downregulation of synaptic strength (Pak 2003 Science), which may be a protective mechanism against toxic runaway excitation. The epilepsies are characterized by recurrent seizures, periods of excessive synchronized neural activity. In mesial temporal lope epilepsy (mTLE), seizures originate in or around the hippocampus, and subsequently propagate throughout the brain. The process by which epilepsy develops (epileptogenesis) is thought to involve alterations in hippocampal synaptic function. There are currently no treatments that clearly prevent epileptogenesis. Within the hippocampus, synapses between the dentate gyrus (DG) axons (mossy fibers, MF) and proximal CA3 dendritic spines (thorny excrescences, TE) serve as a checkpoint for information entering the hippocampus (Lee and Queenan 2013 Neuron), acting as homeostatic "gain control" (Chater & Goda 2013 Neuron). Recently, we have observed that kappa opioid receptor (KOR) activity bidirectionally regulates the strength of these gain control synapses in neuronal cultures. Here, we hypothesized that a failure to engage homeostatic DG-CA3 checkpoints is a contributing factor in the development of TLE. To test this hypothesis, we used the amygdala-kindling model of epileptogenesis, in which repeated subconvulsive shocks elicit gradually more severe seizures. While kindling seizures, we systemically administered mice saline, the KOR agonist U50488, or antagonist norBNI. We found that the KOR activation exacerbated seizure progression, while KOR inhibition attenuated seizure progression and severity. Taken together these results suggest that KOR signaling, perhaps due to modulation of MF-TE homeostasis, can be a novel target for combatting mTLE, the most common form of adult acquired epilepsy.

Disclosures: R.L. Dunn: None. **B.N. Queenan:** None. **P.A. Forcelli:** None. **D.T.S. Pak:** None.

Poster

574. Homeostatic Plasticity II

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 574.02/B75

Topic: B.08. Synaptic Plasticity

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NSF GRFP DGE 1106400

Title: Dynamic gap junction networks regulate ipRGC intra-retinal signaling in the developing retina

Authors: *D. ARROYO[1], M. B. FELLER[2];
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Abstract: Prior to photoreceptor maturation, intrinsically photosensitive retinal ganglion cells (ipRGCs) provide a robust light response that drives early visually-guided behaviors. Here, we demonstrate that the ipRGC-mediated light response of the developing mouse retina is dependent on extensive electrical coupling of ipRGCs. First, we found that ipRGCs are electrically coupled not only to other ipRGCs but also to non-intrinsically-photosensitive retinal neurons (non-ipRGCs). Second, ipRGC photocurrents are effectively propagated through gap junctions. Third, blocking gap junctions reduces the number of cells that respond to light. Finally, the extent of coupling was dynamically regulated by spontaneous synaptic activity, such that pharmacological blockade of cholinergic waves of activity led to an increase in the number of both coupled cells and light-responsive cells. This increase in coupling was phenocopied by blocking D1-type dopamine receptors, suggesting that waves lead to dopaminergic modulation of ipRGC gap junctions. In conclusion, the gap junction network of ipRGC and its activity dependent modulation allows for a dynamic light response in the developing retina.

Disclosures: D. Arroyo: None. **M.B. Feller:** None.

Poster

574. Homeostatic Plasticity II

Location: Hall A

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Program#/Poster#: 574.03/B76

Topic: B.08. Synaptic Plasticity

Title: Theoretical model of TMS-cortical plasticity

Authors: *P. K. FUNG[1,2,3], P. A. ROBINSON[2,3,4];
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Dynamics Center, Sydney Med. Sch. - Western, Univ. of Sydney, Sydney, Australia; [4]Ctr. for Integrated Res. and Understanding of Sleep, Glebe, Australia

Abstract: Transcranial magnetic stimulation (TMS) is a promising brain stimulation technique to induce cortical synaptic plasticity for scientific and therapeutic purposes. However, TMS-induced plasticity exhibit many nonlinearities and variabilities, and we have little understanding of the underlying mechanism of TMS. Here we present a mean field synaptic plasticity theory, based on well established neural field theory and synaptic plasticity theory. This theory reproduces experimental results and phenomena, including rTMS of constant frequency, continuous and intermittent theta burst stimulation (cTBS and iTBS), paired associative stimulation (PAS), TMS dosage dependency and inter-subject variability. Thus, we gain insights on the underlying mechanisms of TMS and cortical plasticity, and make recommendations on TMS protocols.

Disclosures: P.K. Fung: None. **P.A. Robinson:** None.

Poster

574. Homeostatic Plasticity II

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Topic: B.08. Synaptic Plasticity

Support: Air Force Office of Scientific Research

Title: Modulating hippocampal plasticity with *in vivo* brain stimulation

Authors: *R. JANKORD[1], J. ROHAN[2];
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Abstract: Investigations into the use of transcranial direct current stimulation (tDCS) in relieving symptoms of neurological disorders and enhancing cognitive or motor performance have exhibited promising results. However, the mechanisms by which tDCS impacts brain function remain under scrutiny. We have demonstrated that *in vivo* tDCS in rats produced a lasting effect on hippocampal synaptic plasticity, as measured using extracellular recordings. *Ex vivo* preparations of hippocampal slices from rats that have been subjected to tDCS of 0.10 mA or 0.25 mA for 30 minutes followed by 30 minutes of recovery time displayed a robust 2-fold enhancement in long term potentiation (LTP) induction accompanied by a 30% increase in paired pulse facilitation (PPF). The magnitude of the LTP effect was greater with 0.25 mA

compared to 0.10 mA stimulations, suggesting a dose-dependent relationship between tDCS intensity and its effect on synaptic plasticity. To test the persistence of these observed effects, animals were stimulated *in vivo* for 30 min at 0.25 mA then allowed to return to their home cage for 24 hours. Observation of the enhanced LTP induction, but not the enhanced PPF, continued 24 hours following completion of 0.25 mA of tDCS. Addition of the NMDA blocker AP-5 abolished LTP in both control and stimulated rats but maintained the PPF enhancement in stimulated rats. The observation of enhanced LTP and PPF following tDCS demonstrates that non-invasive electrical stimulation is capable of modifying synaptic plasticity.

Disclosures: R. Jankord: None. **J. Rohan:** None.

Poster

574. Homeostatic Plasticity II

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Topic: B.08. Synaptic Plasticity

Support: NIH Grant R01 NS061914

Title: Neurons that innervate a single target adopt a different strategy for maintaining synaptic strength than those neurons that innervate multiple targets

Authors: *Z. LU[1], J. BORYCZ[3], A. CHOUHAN[4], Z. LU[3], I. MEINERTZHAGEN[3], G. MACLEOD[2];
[1]Biol. Sci., [2]Florida Atlantic Univ., Jupiter, FL; [3]Dalhousie Univ., Halifax, NS, Canada; [4]Baylor Col. of Med., Houston, TX

Abstract: Synaptic strength sub-serves the plasticity of neural circuits and is highly plastic. Homeostatic mechanisms normally introduce a measure of stability by acting to maintain the strength of some synapses within a narrow range. However, whether all neurons adopt the same mechanisms for maintaining their output is not known, and little is known about the mechanisms for that maintenance. In a field of *Drosophila* larval muscle fibers that are stereotypically innervated by motor neurons we investigated whether neurons that innervate a single muscle fiber (e.g. MN12-Ib) manifest the same homeostatic changes as those that innervate several muscle fibers (e.g. MNSNb/d-Is). For this, we chronically induced synaptic homeostasis in synapses formed by two different motor neurons on the same muscle fiber (number 12), and found that terminals from the two different neurons adopt different strategies for maintaining their output. Terminals of MN12-Ib show an increase in calcium influx sufficient to generate the

observed increase in neurotransmitter release. In contrast, terminals of MNSNb/d-Is show morphological changes such as an increase in total active zone number, total number of mitochondria as well as increase in terminal volume not seen in MN12-Ib terminals. These changes appear to be sufficient to generate the observed increase in neurotransmission. Interestingly, the morphological changes show subcellular specificity, because terminals of the same neuron on other muscle fibers fail to show such morphological changes. This difference suggests that local rather than global signaling is adequate to enact synaptic homeostasis. Although chronic induction of synaptic homeostasis provides ample time for changes in morphology we are not aware of such morphological forms of synaptic homeostasis being described previously.

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Poster

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Topic: B.08. Synaptic Plasticity

Support: 1K99NS089800-01

R01 EY014439

Title: Continuously recorded neurons reveal sleep/wake dynamics of firing rate homeostasis in freely behaving animals

Authors: ***K. B. HENGEN**[1], J. N. MCGREGOR[1], S. D. VAN HOOSER[1], D. B. KATZ[2], G. G. TURRIGIANO[1];
[1]Biol., [2]Psychology, Brandeis Univ., Waltham, MA

Abstract: We have developed tools to continuously record extracellular signals from ensembles of single neurons in freely behaving rats for hundreds of hours during the critical period for ocular dominance plasticity. This approach allows us to examine the same cells across many iterations of naturally occurring activities and arousal states, as well as during developmental and plasticity induced changes that occur on slower time scales than were formerly addressable. Previously, we demonstrated that activity in ensembles of cortical neurons is regulated homeostatically in the freely behaving animal around a firing rate set point. However, without

the ability track the same individual units across many days, we were unable to determine whether firing rate set-points were implemented at the level of individual neurons or only at the level of the network. Here we employ our system to address two open questions in neuroscience. First, we ask whether individual neurons in the freely behaving animal exhibit a firing rate set point. Second, we examine the role of sleep and wake cycles in the expression of firing rate homeostasis in the freely behaving animal. We recorded activity from ensembles of cortical single units in juvenile rats (postnatal days 24-34) continuously for 10 days during a monocular deprivation (MD) paradigm. When examining neurons that were "online" for the entire recording, firing rates dropped during early MD and then rebounded to baseline levels despite continued deprivation. These data suggest that neocortical neurons regulate their firing around an individual set point. We then examined the dynamics of the homeostatic rebound of spontaneous activity (during prolonged MD) as a function of sleeping and waking states. Our data indicate that homeostatic plasticity in the neocortex emerges during bouts of waking and not sleep. These results raise the possibility of unanticipated interactions between animal behavior and the expression of homeostatic plasticity mechanisms.

Disclosures: **K.B. Hengen:** None. **J.N. McGregor:** None. **S.D. Van Hooser:** None. **D.B. Katz:** None. **G.G. Turrigiano:** None.

Poster

574. Homeostatic Plasticity II

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Topic: B.08. Synaptic Plasticity

Support: NIH R01-NS074366

Title: Sleep disruption alters hippocampal filtering dynamics

Authors: *E. WALLACE[1], R. K. MAGANTI[2], M. V. JONES[3];
[1]Neurosci., Univ. of Wisconsin - Madison, Madison, WI; [2]Neurol., [3]Neurosci., Univ. of Wisconsin, Madison, WI

Abstract: Sleep is a function with vast consequences for physiological homeostasis. Perturbations in sleep patterns can disrupt neurological function, as evidenced by the strong interactions between sleep and epilepsy (Semin Neurol. 29:419). The mechanism of seizure propagation and transition from simple to complex seizures, and how this mechanism interacts with sleep patterns remains largely unknown. One possible contributor to this mechanism lies in

the hippocampal formation. The synapses mediating flow of signals through the dentate gyrus (DG), cornu ammonis (CA) 1 and 3 exhibit distinct frequency-dependent modulation of somatic output (Hippocampus. 22:2184). The hypothesis that sleep serves to down-regulate synaptic connections formed and strengthened during waking (Neuron. 81:12-34) suggests that sleep deprivation may impair synaptic homeostasis and result in hyperexcitability. Integrity of frequency-dependent signal modulation in the hippocampus may be important for suppressing seizures, and sleep disruption may deteriorate such filtering, thus allowing propagation of epileptiform activity. Brief sleep deprivation has been shown to temporarily increase slow-wave activity of rebound sleep, a metric of sleep intensity thought to be associated with synaptic pruning (Brain Sci. 3:318). Here, we evaluated synaptic frequency response dynamics in hippocampal slices from C57bl/6 mice, aged P40 ± 3, after a 1 hour novel object sleep disruption (n = 6 slices; 4 animals) and compared to age matched, treatment-naïve controls (n = 3 slices; 3 animals). Population spikes in the CA1 pyramidal layer were recorded in response to 500 ms trains (100 μs, <250 μA) of sequentially increasing frequencies (2-77 Hz) of stimulation of the Schaffer collaterals. Between groups, firing responses showed similar properties at low frequency stimulation, however divergent patterns were observed in response to frequencies greater than 40 Hz, where treated animals had increased spike facilitation at the two highest frequencies tested (60 and 77 Hz; $F(1, 210) = 45.39$ and $F(1, 273) = 35.00$, respectively; $p < 0.0001$) and a delayed onset of spike depression. It remains to be determined if this increase in high frequency facilitation in the CA1 region of non-epileptic animals in response to brief sleep disruption parallels those of epileptic animals, whereby concomitant sleep disruption may underlie the associated increase in epileptiform activity. Future experiments will be directed to further evaluate filtering properties of CA1 and other synaptic fields of the hippocampal formation with regard to conditions of sleep disruption and epilepsy.

Disclosures: **E. Wallace:** None. **R.K. Maganti:** None. **M.V. Jones:** None.

Poster

574. Homeostatic Plasticity II

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Topic: B.08. Synaptic Plasticity

Support: NIH R00 Award NS062738

Title: Mechanisms underlying the reversibility of synaptic homeostasis

Authors: *C. J. NEFF[1], C. FRANK[2];
[1]Interdisciplinary Grad. Program in Neurosci., [2]Anat. and Cell Biol., Univ. of Iowa, Iowa City, IA

Abstract: The ability of a synapse to maintain a physiologically appropriate output is necessary for all modalities of neurological function. Forms of homeostatic plasticity allow synapses to navigate normal processes of development and aging as well as respond to challenges such as disease. Failure to regulate neuronal output could contribute to a number of disease states including ataxia, migraine, and epilepsy. Yet fundamental aspects of homeostatic plasticity remain poorly understood. In this study, we have shown that homeostatic modulation of neurotransmitter release is a reversible process, and we have examined the time course of this reversibility. The *Drosophila* neuromuscular junction (NMJ) is accessible to electrophysiological recording and has a well-established model of homeostatic plasticity. In this model, impairment of muscle sensitivity to glutamate induces a retrograde (muscle-to-nerve) signal that causes a corresponding increase in the amount of presynaptic glutamate released during evoked potentials. We have examined the reversibility of NMJ homeostatic plasticity by temporally controlling glutamate receptor function. For example, by expressing dominant negative glutamate receptors for discrete time periods, we can provide an initial impairment to muscle glutamate sensitivity, which is offset by an increase in glutamate release. When expression of the mutant glutamate receptors is ceased, we find that glutamate release returns to control levels. Interestingly, we also find that the amount of time necessary for glutamate release to return to control levels depends on the extent of the initial glutamate receptor impairment. The NMJ can execute a homeostatic modulation of neurotransmitter release in the opposite direction as well. When the *Drosophila* vesicular glutamate transporter (dVGlut) is overexpressed in neurons, there is an enhancement in quantal size and a compensatory homeostatic decrease in quantal content. We have begun to characterize the reversibility of dVGlut-induced decreases in quantal content. Finally, data will be shared from an ongoing genetic screen we are conducting to identify molecules that are necessary to bring vesicle release back to control levels once homeostatic challenges to NMJ function are removed.

Disclosures: C.J. Neff: None. **C. Frank:** None.

Poster

574. Homeostatic Plasticity II

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Topic: B.08. Synaptic Plasticity

Support: NIH Grant R01NS065992

Whitehall Grant 2010-05-42

Title: Nicotinic receptor modulation triggers bidirectional synaptic scaling in embryonic motoneurons *in vivo*

Authors: *C. E. GONZALEZ-ISLAS, M. GARCIA-BEREGUIAIN, P. A. WENNER; Emory Univ. Sch. Med., Atlanta, GA

Abstract: When external challenges modify baseline firing rate in a neuronal network, a set of mechanisms is prompted to restore spiking to its original rate. One of these homeostatic mechanisms is believed to be synaptic scaling, which consists of adjustments in the strength of all synapses onto a neuron in order to stabilize its firing rate. While changes in spike rate are thought to trigger synaptic scaling, an alternative possibility is that changes in neurotransmitter receptor activation could directly trigger this form of plasticity. Since spiking and transmission are necessarily coupled, it has been difficult to separate their independent roles in triggering the scaling process. Recently, we have reported findings that suggest reduced transmission directly triggered cell-wide synaptic upscaling in cortical neurons *in vitro* (Nat Commun 2015. 6:6339). The current study intended to test if alterations in neurotransmission, rather than spiking, could also trigger scaling in the living embryonic spinal network. Previously we have shown that blocking spiking or $GABA_A$ receptors ($GABA_ARs$) in ovo for two days triggered synaptic upscaling of both AMPA- and GABAergic synapses (PNAS. 2008. 105:32 11412-17). Both perturbations reduce spiking and GABAergic transmission, so either could trigger scaling. We therefore independently manipulated spiking activity and $GABA_AR$ activation *in ovo* to better identify the trigger for synaptic scaling. To do this we took advantage of our recent finding that nicotinic receptors (nAChRs) presynaptically modulate the release of GABA vesicles. Our results suggest that presynaptic modulation of GABA release by modulation of nAChR activation can trigger bidirectional synaptic scaling, while dramatic changes in spiking activity have little effect. Further, we find the striking result that scaling can be fully achieved by simply altering the frequency of spontaneous release events, which are not dependent on action potentials. If changes in $GABA_AR$ activation due to action potential-independent GABA release were the trigger, then scaling would have little to do with spiking, and would not serve as an effective feedback control for the maintenance of spike rate.

Disclosures: C.E. Gonzalez-Islas: None. **M. Garcia-Bereguiain:** None. **P.A. Wenner:** None.

Poster

574. Homeostatic Plasticity II

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Topic: B.08. Synaptic Plasticity

Support: NIH Grant K01MH097961

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Title: Glutamatergic signaling regulates potentiation of specific GABAergic synapse

Authors: *C. Q. CHIU, M. J. HIGLEY;
Dept. of Neurobio., Yale Univ. Sch. of Med., New Haven, CT

Abstract: Although it is known that strong glutamatergic activity can modify the strength of GABAergic synaptic transmission, the underlying cellular mechanisms are not well understood. This question is complicated by the great diversity of GABAergic interneurons, which may exhibit heterogeneous rules for altering their synaptic weights. Here, we utilize cell type-specific optogenetic stimulation in mouse prefrontal cortical slices to study the capacity of GABAergic synapses formed by different interneuron subtypes to exhibit activity-dependent plasticity. We find that brief activation of NMDA-type glutamate receptors (NMDARs) increases dendritic inhibition mediated by somatostatin-expressing interneurons (SOM-INs) but does not alter perisomatic inhibition arising from parvalbumin-expressing interneurons (PV-INs). Potentiation of dendritic inhibition (SOM-iLTP) requires postsynaptic activation of NMDARs, a rise in intracellular calcium, and activation of CaMKIIa. Similar potentiation of dendritic inhibition evoked by optical uncaging of GABA indicates that SOM-iLTP is expressed postsynaptically. We further show that postsynaptic activation of CaMKIIa selectively modulates GABAergic synapses formed by SOM-INs while leaving PV-IN synapses unchanged. This specificity may be mediated by the selective expression of beta3-subunit-containing GABA-A receptors at SOM-IN synapses, as evidenced by their sensitivity to the anesthetic agent etomidate. Finally, we find that NMDAR signaling *in vivo* is required for the maintenance of dendritic inhibition. Our results indicate that the molecular differences between subpopulations of GABAergic synapses confer a differential capacity for glutamatergic regulation in the neocortex.

Disclosures: C.Q. Chiu: None. **M.J. Higley:** None.

Poster

574. Homeostatic Plasticity II

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Title: Quantitative ultrastructural dissection of cryo-fixed synapses using high-resolution electron tomography

Authors: *C. TAO[1], Y. LIU[1], R. SUN[1], B. ZHANG[1], J. ZHANG[1], P. LAU[1], Z. ZHOU[2], G. BI[1]; [1]Univ. of Sci. and Technol. of China, Anhui, China; [2]UCLA, Los Angeles, CA

Abstract: Functional heterogeneity of neuronal synaptic transmission and plasticity must stem from diverse molecular architectures and subcellular organizations. Using cryo electron tomography (cryoET) capable of capturing three dimensional subcellular ultrastructures in their native state at nanometer resolution, we have visualized *in situ* organization of macromolecules and organelles of various synapses in intact hippocampal neurons grown in culture. Semi-automated segmentation and quantitative analysis revealed fine details of synaptic architecture, including vesicular populations in the presynaptic bouton, cell adhesion molecules in the synaptic cleft, as well as postsynaptic density, actin filaments and ribosomes in the postsynaptic compartment. In order to determine the identity of glutamatergic and GABAergic synapses, we developed a convenient cryo-stage and a high-precision algorithm for correlative light and electron microscopy (cLEM), which allowed us to determine distinct shapes of the postsynaptic densities corresponding to different synaptic types. Finally, we observed altered synaptic ultrastructure following chronic neuronal inactivation characterized by a marked increase in the number of presynaptic dense core vesicles, indicating a new structural mechanism that may underlie homeostatic synaptic plasticity.

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Poster

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Support: CONICYT Anillo ACT-1113

FONDECYT 1120580 (BM)

FONDECYT 11140430 (CR)

CONICYT 79140056(CR)

Title: Excitability modulation of CA1 neuron by TRPV1 channels activation

Authors: *C. A. ROZAS[1], C. MAUREIRA[2], R. DELGADO[1], B. MORALES[1];
[1]Univ. of Santiago de Chile, Santiago, Chile; [2]Univ. de Chile, Santiago, Chile

Abstract: The functional properties of TRPV1 channels have been described mainly in the nocioceptive neurons of peripheral nervous system. TRPV1 channels are also present at central nervous system where the signaling and functional properties are less well known. At the hippocampus, TRPV1 channels regulate long-term plasticity (LTP and LTD) by modulating the GABAergic system. Moreover, several studies involve TRPV1 channels in network excitability. In the pilocarpine-induced model of epilepsy, TRPV1 protein levels increase in the dentate gyrus of hippocampus. TRPV1 agonists induce temporal lobe epilepsy in a mice model. Additionally, human patients of mesial temporal lobe epilepsy, also display increased expression of TRPV1 channels in temporal cortex and hippocampus. However TRPV1 channels role in CA1 excitability properties has not been addressed. Here, we evaluated the effect of pharmacological activation of TRPV1 channels on excitability of CA1 hippocampal neurons. We observed that TRPV1 channels agonists induces a threshold hyperpolarization and shortening of action potentials duration. This changes correlated with an increase on excitability on the f vs I transfer function, as well as a broad network excitability increase; nevertheless this changes do not associate with changes in the input resistance of neurons.

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Poster

574. Homeostatic Plasticity II

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Topic: B.08. Synaptic Plasticity

Support: NIH Grant R01NS090644

NIH Grant T32NS007433-17

Title: Homeostatic regulation of presynaptic neurotransmitter release in the vertebrate neuromuscular synapse

Authors: *A. E. HOMAN, G. E. RIBBLE, S. D. MERINEY;
Neurosci., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Homeostatic synaptic plasticity is an essential process by which a synapse is able to regulate its excitability to compensate for perturbations to the system. Homeostatic changes to postsynaptic receptors following alterations in activity have been well studied at central nervous system synapses, however less attention has been paid to presynaptic effects. Presynaptic homeostatic plasticity centers on the mechanisms by which the nerve terminal alters neurotransmitter release in response to either reduced or enhanced postsynaptic activity. While presynaptic homeostatic plasticity has been well characterized in *drosophila*, this form of plasticity has not been well studied at vertebrate synapses. Here we explore homeostatic regulation of neurotransmitter release at the vertebrate neuromuscular junction synapse. Following acute partial block (30-60 minutes) of postsynaptic nicotinic acetylcholine receptors, we observed a compensatory increase in quantal content (QC). We did not observe an increase in quantal amplitude, suggesting a presynaptic locus for modulation. Additionally, we observed a dramatic increase in short-term depression during a 50 Hz stimulus train over 10 stimuli, further supporting the conclusion that short-term partial postsynaptic receptor blockade increases the probability of neurotransmitter release. These data provide evidence that presynaptic modulation of neurotransmitter release can occur on a brief time scale in a vertebrate neuromuscular junction. The mechanisms for such plasticity, and the retrograde signal that induces presynaptic change following a postsynaptic receptor blockade are currently being studied. These changes are reminiscent of what has previously been observed at the human neuromuscular junction where quantal content appears to be larger in neuromuscular junctions from myasthenia gravis patients (who have fewer postsynaptic receptors) as compared to healthy individuals (Cull-Candy et al., 1980, J. Physiol., 299: 621). Overall, presynaptic homeostatic plasticity is likely to be an important adaptation that contributes to physiological alterations in synaptic activity, disease adaptations, and treatment effects.

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Poster

574. Homeostatic Plasticity II

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Topic: B.08. Synaptic Plasticity

Support: NIH Grant NS039313

Title: Evidence that mctp is presynaptic calcium sensor necessary for robust homeostatic plasticity

Authors: O. GENC[1], D. K. DICKMAN[2], W. MA[2], A. TONG[1], *G. W. DAVIS[1];
[1]Dept Biochem & Biophysics, Univ. California-SF, San Francisco, CA; [2]Neurobio., USC, Los Angeles, CA

Abstract: Homeostatic signaling systems are believed to interface with the mechanisms of neural plasticity to ensure stable neural function throughout life. At the neuromuscular junction of organisms ranging from *Drosophila* to human, inhibition of postsynaptic neurotransmitter receptor function is offset by a compensatory increase in presynaptic neurotransmitter release, restoring normal muscle excitation. This is referred to a presynaptic homeostatic plasticity (PHP). It is widely speculated that impaired or maladaptive PHP will participate in the cause or progression of diverse neurological disease states. However, a clear link to disease will necessitate a molecular understanding of PHP. We are pursuing a forward genetic screen based on synaptic electrophysiology to identify genes that, when mutated, block PHP. In this screen, we identified mutations in the mctp gene (Multiple C2 Domain and Transmembrane Region Protein). MCTP is highly conserved from *Drosophila* to human and has a unique structure comprised of two transmembrane regions and three cytoplasmic C2 domains. We have identified multiple mutations in the *Drosophila* mctp gene, including molecular null mutations generated by CRISPR/Cas9-mediated mutagenesis. Loss of mctp causes a statistically significant decrease in presynaptic neurotransmitter release that is rescued by transgenic neuron-specific expression of UAS-mctp in the mctp mutant background. We then demonstrate that MCTP is necessary in motoneurons for both the rapid induction and sustained expression of PHP. An epitope-tagged MCTP transgene that is sufficient to rescue PHP in the mctp mutant background is found to localize on a highly reticulated system of membranes that extend continuously along the motoneuron axons and throughout the presynaptic nerve terminal. We speculate that MCTP is localized on the presynaptic endoplasmic reticulum where it functions as a calcium sensor and/or calcium buffer that is essential for normal neurotransmitter release and presynaptic homeostatic plasticity.

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Poster

575. The Dynamic Synapse

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Support: NCCR SYNAPSY operating grant

Title: Cocaine occludes bidirectional synaptic plasticity between medium-sized spiny neurons of the nucleus accumbens and ventral pallidum projection neurons

Authors: *M. CREED, C. LÜSCHER;
Univ. of Geneva, Geneva, Switzerland

Abstract: Meaghan Creed, Christian Lüscher The ventral pallidum (VP) is a structure critically involved in hedonic and motivational processing of both natural rewards and of drugs of abuse. It is the primary output of the nucleus accumbens (NAc), receiving projections from D1- and D2-dopamine receptor expressing medium sized spiny neurons (D1- D2-MSNs), and projecting on to other brain regions involved in reward processing, such as the ventral tegmental area (VTA). Our group has previously shown that D1 and D2 MSNs in the NAc undergo distinct forms of synaptic plasticity following cocaine exposure (Pascoli et al., Nature 2011, 2014). Classical pharmacology and ablation studies have implicated the NAc and the VP in both the liking and wanting of natural rewards; both of these phenomena are decreased following exposure to cocaine (Smith et al., Behav Brain Res, 2009). In this study, we used mutated channel rhodopsin (chETA; capable of following stimulation frequencies of up to 100 Hz) expressed selectively in D1- or D2-MSNs of the NAc shell to dissect the contribution of each of these projections to cocaine-evoked plasticity in the VP. Consistent with previous studies (Kupchik et al., J Neurosci, 2014), we found that following passive cocaine exposure, inhibitory tone onto VP neurons was increased and there was an occlusion of inhibitory long-term potentiation (iLTP) induced by electrical high-frequency stimulation. We report that D1- and D2-MSNs project to the VP in roughly equal proportion and we describe opposing forms of synaptic plasticity at synapses between D1- and D2-MSNs and VTA-projecting VP neurons. Specifically, and in agreement with previous work, high-frequency stimulation applied selectively at of D1-MSN inputs to the VP induces LTP of these inputs (Bocklisch et al., Science, 2013) whereas and the same stimulation protocol applied at D2-MSNs induced a long-term depression (iLTD) at the stimulated inputs. These two forms of activity-dependent plasticity were expressed by distinct mechanisms and, importantly, both forms of plasticity were occluded by cocaine treatment. Finally, by optogenetically manipulating D1- and D2-projections to VP neurons we explore the

causal role of each projection in the decreased hedonic impact and drive to obtain a natural reinforcer following cocaine treatment.

Disclosures: **M. Creed:** None. **C. Lüscher:** None.

Poster

575. The Dynamic Synapse

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 575.02/B89

Topic: B.08. Synaptic Plasticity

Title: Regulation of local calcium dynamics at a reciprocal synapse

Authors: *C.-T. JUAN, M. HENDRICKS;
Dept. of Biology, IPN, McGill Univ., Montreal, QC, Canada

Abstract: Calcium plays diverse roles in neuronal function, and calcium dynamics are under precise spatiotemporal control. We recently characterized complex calcium dynamics in a pair of interneurons called RIA in *C. elegans*. We observed overlapping calcium events comprising local mobilization of internal stores, regulated by metabotropic acetylcholine receptors, and whole-cell events resulting from depolarization. These two types of events represent motor and sensory circuit activity, respectively, and interact on behavioural time scales to contribute to the regulation of head movements and locomotion. We are now characterizing the molecular mechanisms for establishing and regulating the spatial and temporal properties of local calcium events and their affect on pre- and post-synaptic function. Our results suggest that RIA compartmentalized calcium dynamics share molecular mechanisms with the regulation of local calcium events and plasticity in dendritic spines in mammalian neurons, in particular the involvement of ryanodine-sensitive pools and the role of plasma membrane Ca^{2+} ATPases in regulating calcium dynamics.

Disclosures: **C. Juan:** None. **M. Hendricks:** None.

Poster

575. The Dynamic Synapse

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 575.03/B90

Topic: B.08. Synaptic Plasticity

Title: A possible role for REM sleep in synaptic plasticity: Opposed changes in the CA3-CA1 and hippocampus-to-Nucleus Accumbens connections during sleep states

Authors: *J. CARPONCY[1], N. FRAIZE[2], P.-A. LIBOUREL[2], G. MALLERET[2], P. SALIN[2], R. PARMENTIER[2];
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Abstract: Numerous theories have been elaborated to explain how different sleep stages and oscillations may regulate synaptic plasticity and memory. However, studies showing modulations of synaptic efficacy during sleep-wake cycles are scarce; especially at connections linking areas involved in memory. It has been proposed that a loop between the hippocampus (Hpc), the Ventral Tegmental Area (VTA), and the Nucleus Accumbens (NAc) could be crucial for the consolidation of salient memories (Lisman and Grace, 2005). Therefore, we decided to focus on the synaptic transmission within Hpc and between Hpc and NAc, during sleep. More precisely, we examined the dynamics of synaptic changes in the connections linking these areas during the three vigilance states: Waking (Wk), Slow-Wave Sleep (SWS), and Paradoxical Sleep (PS or REM sleep). We recorded Excitatory Post-Synaptic Potentials (fEPSP) at the Schaffer Collaterals of the Hpc (CA3-CA1) and in the NAc after stimulation of the fornix, in freely-moving rats during several days. CA3-CA1 and Hpc-NAc synapses were differently affected by the vigilance states. CA3-CA1 synaptic responses increased during SWS but decreased during PS, in comparison to Wk. In contrast, we found that Hpc-NAc fEPSP responses were significantly increased during PS compared to Wk and SWS. Thus, PS appears to be a privileged state for the information transfer between Hpc and NAc, although SWS may facilitate the intra-hippocampal communication. Altogether, these dissociations during different sleep stages may be crucial for the cognitive purposes sustained by the Hpc-NAc-VTA loop. Thus, these findings could help to decipher the functions that sleep could have in the information transfer during memory consolidation and in the reinforcement of salient memories.

Disclosures: J. Carponcy: None. **N. Fraize:** None. **P. Libourel:** None. **G. Malleret:** None. **P. Salin:** None. **R. Parmentier:** None.

Poster

575. The Dynamic Synapse

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 575.04/B91

Topic: B.08. Synaptic Plasticity

Support: VTCRI startup funds

Title: Differential effects on somatic and dendritic inhibition in PFC layer V pyramidal cells by emotional trauma

Authors: L. LIU, W. ITO, *A. Y. MOROZOV;
Virginia Tech. Carilion Res. Inst., Roanoke, VA

Abstract: Stressful events increase susceptibility of developing psychiatric disorders such as PTSD. Previous studies have shown that mice exhibit enhanced contextual fear learning and passive avoidance learning, after they observe cagemates but not strangers receiving electric foot shocks in the observational fear paradigm. The forms of fear learning enhanced by observational fear require activity of the prefrontal cortex (PFC). However, it is unknown whether the PFC circuits undergo plastic changes, which could potentially be responsible for the behavioral changes. The aim of this study was to identify changes of glutamatergic and GABAergic synaptic transmissions in mouse PFC 12 hours after observational fear. Using whole-cell recording in brain slices from 60-80 day old mice, we found that EPSPs evoked in PFC layer V pyramidal cells by 5 Hz trains of electric stimulation of PFC layer I were facilitated more strongly along the train and that neurons fired more action potentials during the stimulation in emotionally traumatized mice. These differences were no longer detected in the presence of picrotoxin (100 μM), a GABAa receptor inhibitor, suggesting that observational fear altered GABAergic rather than glutamatergic transmission. Consistently, IPSCs recorded in PFC layer V pyramidal cells exhibited more depression during 5 Hz train of electrical stimulation in observational fear group. Surprisingly, dendritic IPSCs, isolated by puffing picrotoxin on the soma of the recorded cell, showed less depression during 5 Hz train of electrical stimulation. Moreover, the differences between observational fear and control groups were eliminated with bath application of CGP 52432, a GABAb receptor inhibitor. To further test the effect on somatic and dendritic IPSCs, we used optogentics to selectively stimulate either somatically projecting parvalbumin (PV) interneurons or distally projecting somatostatin (SOM) interneurons in PFC. For observational fear group, IPSCs evoked by 5 Hz optical stimulation of PV interneurons showed more depression, while the ones from SOM interneurons showed less depression. These findings suggest that in mice after emotional trauma the balance of inhibition shifted from soma to distal dendrites in PFC layer V pyramidal cells. This may allow inputs to PFC deep layer to have stronger impact on PFC layer V pyramidal cells than inputs to superficial layer.

Disclosures: L. Liu: None. **W. Ito:** None. **A.Y. Morozov:** None.

Poster

575. The Dynamic Synapse

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 575.05/B92

Topic: B.08. Synaptic Plasticity

Support: JHU,Science of Learning Insti

Title: Regulation of synaptic plasticity by the dark/light cycle

Authors: *K. HE[1], S. HATTAR[2], A. KIRKWOOD[3];
[1]Mind/Brain Inst., The Johns Hopkins Univ., Baltimore, MD; [2]Dept. of Neurosci. (JHMI),Department of Biol., [3]The Zanvyl Krieger Mind/Brain Institute,The Solomon H. Snyder Dept. of Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: Normal sleep is crucial for learning and memory formation. Moreover, a wealth of evidence indicates that the learning-related changes in synaptic connectivity initiated during the waking states are further consolidated and enhanced during the sleep stages. Most likely these synaptic changes require activity-dependent forms of plasticity such as long-term potentiation (LTP) and depression (LTD). Indeed, manipulations that disrupt the induction of LTP and LTD also prevent the consolidation of learning during sleep. In this context, it is well established that sleep-deprivation severely impairs the induction and expression of LTP. However, whether LTP and LTD are regulated by the natural sleep/wake cycle is still unclear. As a step into that direction we compared LTP/LTD in acute hippocampal slices harvested from mice that were sacrificed at the end of either the 12 h DARK cycle (mostly awake) or the 12 h LIGHT cycle (mostly sleep).We found that the magnitude of LTP and LTD is greatly reduced at the end of the light cycle, consistent with the idea that LTP/LTD-like activity is recruited to consolidate learning and memory during sleep.

Disclosures: K. He: None. **S. Hattar:** None. **A. Kirkwood:** None.

Poster

575. The Dynamic Synapse

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 575.06/B93

Topic: B.08. Synaptic Plasticity

Support: CIHR Grant MOP 15685

Title: Hippocampal theta rhythm provides different modulation of long-term potentiation and spike excitability at the basal and apical dendrites of hippocampal CA1 pyramidal cells

Authors: C. S. H. LAW[1], *L. LEUNG[2];
[1]Physiol. and Pharmacol., [2]Univ. Western Ontario, London, ON, Canada

Abstract: The hippocampal theta rhythm facilitates memory formation. This study investigated the temporal relation of long-term potentiation (LTP) with the hippocampal theta rhythm. Theta rhythm consists of a wave of somatodendritic depolarization, but the depolarization of apical and basal dendrites of hippocampal CA1 pyramidal cells peak at a similar theta phase (Leung, J Neurophysiol 52: 1051). Thus, we hypothesize that the population spike excitability evoked by excitation of the apical and basal dendrites peak at a similar phase of the theta rhythm. We also expect that LTP at the basal and apical dendritic synapses to be maximal at a similar theta phase. Previous studies reported apical dendritic LTP at the peak of the apical dendritic theta, but did not quantify the relation between LTP and theta phase. Rats (~300 g) were anesthetized by urethane. Stimulating electrodes were placed in stratum radiatum and stratum oriens, to excite apical and basal dendrites of CA1 pyramidal cells, respectively. A 16-channel electrode array (50 μm between electrodes) recorded field potentials in CA1. Burst stimulation (5 pulses at 200 Hz, 3 x response threshold) was used to induce LTP, and a single pulse (~1.5x population spike threshold) was used to evoke a population spike. Apical (or basal) LTP was measured by the rising slope of the excitatory current sink at the apical (or basal) dendritic layer. Theta phase was derived from the theta field potentials recorded at stratum lacunosum-moleculare (90° = positive peak). Maximal population spikes evoked by single-pulse stimulation of the apical and basal dendrites occurred at the falling phase of theta (120°-160°). LTP was maximal when the burst stimulation occurred during the rising phase of theta, which was 306°-30° (basal LTP) and 333°-24° (apical LTP). The magnitude of LTP decreased gradually when tetanized at a phase different from the optimal phase. For the LTP averaged 30-120 min, there was a significant linear correlation of the LTP with deviation from the optimal phase [basal: $R2=0.23$; $p<0.05$; $N=25$, and apical: $R2=0.31$; $p<0.01$]. We conclude that theta rhythm sets up a temporal (or phase) gradient of synaptic plasticity at the basal and apical dendrites of hippocampal pyramidal cells. Both basal and apical LTP were optimal during the rising phase of the distal apical dendritic theta rhythm, distinctly different from the phase of maximal spike excitability that occurs in the falling theta phase. Possible mechanisms will be discussed.

Disclosures: C.S.H. Law: None. **L. Leung:** None.

Poster

575. The Dynamic Synapse

Location: Hall A

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Program#/Poster#: 575.07/B94

Topic: B.08. Synaptic Plasticity

Support: Air Force Office of Scientific Research

Title: The effect of tissue on current shunting during anodal tDCS

Authors: *M. P. JACKSON, W. TUCKER, R. JANKORD;
Wright Patterson AFB, Wright Patterson AFB, OH

Abstract: Jackson M, Tucker W, Jankord R Transcranial Direct Current Stimulation (tDCS) is a non-invasive, inexpensive method of treating various psychological diseases, as well as improving memory and cognition. The purpose of this study was to examine the impact of tissue on current shunting during anodal tDCS *in vivo.* This study compares *in vivo* brain changes from anodal tDCS when an electrode is placed on the skull versus on the skin. Anodal tDCS was applied to Sprague-Dawley rats for 60 minutes. The anodal electrode (25 mm^2, 0.00 mm to -5.00 mm Bregma) was applied to the skull utilizing the following current densities (A/m^2): Sham (n=4), 6 (n=4), 12 (n=4), 20 (n=3), 40 (n=4), and 100 (n=3). tDCS was applied to the scalp utilizing the following current densities: Sham (n=2), 20 (n=3), 40 (n=3), and 100 (n=3). Slide mounted 16 μm thick brain tissue was processed for histological examination using Hematoxylin and Eosin (H&E) staining. Histological effects were quantified using an Olympus BX-63 microscope with Q100 Blue Camera and CellSens software. Stimulation of the skull showed a reduction or absence of cortical tissue occurring at 20 A/m^2, having an affected volume of 0.17 mm^3. At 40 A/m^2 and 100 A/m^2, the average affected volume within groups was 6.76 mm^3 and 13.01 mm^3, respectively. When these same current densities (20, 40, and 100 A/m^2) were applied to the scalp, no evidence of cortical histological alteration was observed. This study showed that brain tissue alterations from anodal tDCS can occur at 20 A/m^2 when the electrode is placed on the skull, which is less than the tDCS safety threshold previously identified. Our *in vivo* model showed no histological differences between scalp tDCS groups, consistent with predictions of the tDCS computational models. These results show skin tissue significantly attenuates the effect of current density on the brain, and that skin tissue will shunt a portion of tDCS current when the electrode is placed on the scalp.

Disclosures: M.P. Jackson: None. **W. Tucker:** None. **R. Jankord:** None.

Poster

575. The Dynamic Synapse

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Topic: B.08. Synaptic Plasticity

Support: US Office of Naval Research Global (ONRG) (grant N62909-15-1-2002)

Italian Ministry of Health (GR-2011-02349998)

Università Cattolica (D.1 funds)

Title: Anodal transcranial direct current stimulation improves hippocampal-dependent learning and memory by boosting synaptic plasticity through epigenetic modulation of Bdnf gene

Authors: *M. V. PODDA[1], S. COCCO[1], A. MASTRODONATO[1], S. FUSCO[1], L. LEONE[1], S. A. BARBATI[1], C. COLUSSI[2], M. MAINARDI[1], C. RIPOLI[1], C. GRASSI[1];
[1]Inst. of Human Physiology, Univ. Cattolica, Rome, Italy; [2]Inst. of Cell Biol. and Neurobiol., Natl. Res. Council, Rome, Italy

Abstract: In recent years several clinical trials have suggested that transcranial direct current stimulation (tDCS) improves cognitive and motor functions in healthy subjects as well as in patients with neurological and neuropsychiatric diseases. However upon which neural substrates tDCS acts in the brain and how exactly this technique modulates brain activity is still poorly understood. We previously demonstrated that *in vitro* DCS of acute hippocampal slices induced polarity-dependent modulation of long-term potentiation (LTP) at Schaffer collateral (CA3)-CA1 synapses (Ranieri et al., 2012). The present study investigated the impact of anodal tDCS on hippocampal synaptic plasticity in mice at electrophysiological, molecular and behavioral levels. Results showed that LTP at CA3-CA1 synapses was increased in hippocampal slices from mice receiving anodal tDCS (350 μA for 20 min). Interestingly 24 h and 1 week after tDCS-mice showed enhanced hippocampal-dependent learning and memory assessed by Morris water maze and novel object recognition tests. Significant molecular changes were detected in the hippocampi of tDCS-mice compared to sham-stimulated controls. They included: i) enhanced phosphorylation of CAMKII and CREB (pCREB133); ii) pCREB binding to the Bdnf promoter I and recruitment of the HAT CBP to the same promoter; iii) S-nitrosylation of HDAC2. Activation of CBP and inhibition of HDCA2 could account for enhanced H3K9 acetylation on Bdnf promoter I and consequent increase of Bdnf expression that we detected 24 h and 1 week after tDCS at both mRNA and protein levels. Epigenetic regulation of Bdnf expression by tDCS was confirmed by results showing that the HAT inhibitor curcumin prevented tDCS-induced increase in Bdnf mRNA and protein expression as well as memory enhancement. Suppression of

Bdnf signaling with the TrkB receptor antagonist, ANA-12, similarly occluded tDCS-effects on memory, thus supporting the role of this neurotrophin in mediating tDCS effects on hippocampal plasticity. Data reported here advance our knowledge on the neural substrates responsible for tDCS-dependent enhancement of learning and memory that is of key importance for the implementation of non-invasive brain stimulation techniques in routine clinical practice. Furthermore, our results lend support to use tDCS to treat a wide range of brain diseases associated to impaired neuroplasticity.

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Poster

575. The Dynamic Synapse

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Topic: B.08. Synaptic Plasticity

Support: Neurological Foundation of New Zealand, Project grant (J.N.J Reynolds & J.B.H Shemmell)

Rutherford Discovery Fellowship (J.N.J Reynolds)

University of Otago Doctoral Scholarship (N Matheson)

Title: The effects of transcranial magnetic stimulation on single neurons: Evidence for induced changes in synaptic function and excitability

Authors: *N. MATHESON[1], J. B. H. SHEMMELL[2], P. W. BROWNJOHN[2], J. N. J. REYNOLDS[1];
[1]Dept. of Anat., [2]Sch. of Physical Educ. Sport and Exercise Sci., Univ. of Otago, Dunedin, New Zealand

Abstract: Transcranial magnetic stimulation (TMS) is applied to the human brain in order to non-invasively activate neural circuits. Under certain circumstances, repetitive TMS (rTMS) can alter the activity of these circuits for a time outlasting the stimulation period, as evidenced by changes in peripheral motor-evoked potentials (MEPs). In addition to gross changes in cellular excitability, these prolonged changes have been interpreted as due to the induction of synaptic plasticity. At a single neuron level however, the effects of rTMS are not well understood and the

induction of synaptic plasticity or prolonged changes in cellular excitability have not been demonstrated. We used a rat model to study the effects of TMS on membrane potentials of single pyramidal neurons and subthreshold monosynaptic responses. *In vivo* intracellular sharp-electrode electrophysiological recordings were made from single cortical neurons in urethane-anaesthetized Wistar rats, during the application of TMS. Spontaneous neuron activity was recorded in response to single pulse and rTMS. In addition, post-synaptic potentials (PSPs) elicited using electrical or magnetic stimulation of the ipsilateral hemisphere were investigated both pre and post rTMS. Single pulse TMS consistently elicited both PSPs and action potentials in spontaneously active cortical pyramidal neurons. These responses were reliably obtained following stimulation at rTMS intensities much lower than those used in many clinical settings. During rTMS trains, spontaneous rhythmical neuronal activity was disrupted and in many cases neuronal firing was induced. Following rTMS, neuronal excitability was altered as indicated by lasting changes in rheobase current. Furthermore, long term potentiation (LTP) was induced using intermittent theta burst stimulation. These results provide the first indication of the effects that both single pulse and repetitive TMS have on cortical neuron excitability and synaptic plasticity. With a better understanding of these effects it is hoped rTMS protocols may be more effectively targeted to specific neural circuits, in order to optimize clinical treatment of neurological disorders.

Disclosures: N. Matheson: None. **J.B.H. Shemmell:** None. **P.W. Brownjohn:** None. **J.N.J. Reynolds:** None.

Poster

575. The Dynamic Synapse

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Topic: B.08. Synaptic Plasticity

Support: Compagnia di San Paolo

Title: Coordinated plasticity at inhibitory and excitatory synapses

Authors: T. RAVASENGA, *A. BARBERIS;
Istituto Italiano Di Tecnologia, Genoa, Italy

Abstract: Learning and memory are believed to depend on plastic changes of neuronal circuits due to activity-dependent potentiation or depression of specific synapses. Traditionally, inhibitory synapses were assumed to be relatively invariant to ensure reliable control of the

neuronal and network plasticity was hypothesized to mainly rely on the flexibility of glutamatergic excitatory synapses. Nevertheless, an increasing body of evidence has revealed that inhibitory synapses undergo several types of plasticity at both pre- and post- synaptic levels. Here, we characterized a form of postsynaptic potentiation (iLTP) induced by depolarizing protocols delivered to pyramidal cells in hippocampal cultures. We show that 40 sec depolarizing pulses (0 mV) applied to the postsynaptic neuron induced a stable IPSCs potentiation that persisted up to 45 minutes. We observed that similar potentiation of GABAergic current amplitude was induced by postsynaptic low frequency stimulation (2 Hz). We demonstrated that this form of iLTP was CaMKII dependent, in line with recent studies showing the involvement of CaMKII in a specific form of chemical GABAergic postsynaptic potentiation (chem-iLTP). Intriguingly, CaMKII is also crucial for LTP of glutamatergic synapses mediated by synaptic accumulation of AMPA receptors at postsynaptic site. This shared molecular determinant suggests a potential source of interplay between plasticity occurring at GABAergic and glutamatergic synapses. Such "plasticity coordination" is expected to be crucial for the balance of dendritic excitation vs. inhibition (E/I) during network activity. We observed here that the aforementioned depolarizing protocols induced depression at glutamatergic synapses (LTD), indicating a non-homeostatic relation between inhibitory and excitatory plasticity. In order to further explore this issue we investigated how plasticity induced at glutamatergic spines interferes with the strength of GABAergic synapses by using a glutamate UV-laser uncaging approach. We report here that glutamatergic LTP heterosynaptically affects the GABAergic synaptic strength at single synapse level. Our findings suggest that E/I balance can be selectively tuned in spatially restricted dendritic sub regions.

Disclosures: T. Ravasenga: None. **A. Barberis:** None.

Poster

575. The Dynamic Synapse

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Topic: B.08. Synaptic Plasticity

Support: NIH Grant DA033150

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Title: Morphine induces synaptic impairment in cultured hippocampal neurons: reversal with platelet-derived growth factor

Authors: *Y. CAI[1], H. LIU[2], H. XIONG[2], J. ARIKKATH[3], S. BUCH[2];
[2]Dept. of Pharmacol. and Exptl. Neurosci., [3]Munroe-Meyer Inst. & Dept. of Pharmacol. and Exptl. Neurosci., [1]Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: Chronic exposure to morphine often leads to reductions in spine density culminating into functional impairment of learning and memory. Strategies aimed at reversing the synaptodendritic injury are thus warranted in the field. PDGF is a pleiotropic growth factor that is involved not only in embryonic development but also plays a vital role in neuronal proliferation/differentiation during adulthood. Previous studies have demonstrated that PDGF-BB exerts its neuroprotective effect via the induction of synaptic plasticity gene Arc. The goal of this study was to explore the role of morphine in mediating synaptodendritic injury and the neuroprotective role of PDGF-BB in restoring this defect. Our findings demonstrated that morphine via its binding to the mu opioid receptor mediated the reduction of spine density and the excitatory synaptic marker vGlut1 with a concomitant upregulation of inhibitory synaptic marker GAD65 in rat primary hippocampal neurons. Morphine also elicited oxidative stress via the NADPH oxidase-dependent generation of reactive oxygen species (ROS), which also was critical for morphine-mediated synaptic impairment. Neuronal endoplasmic reticulum (ER) stress induced by morphine was essential for synaptic injury, and this effect was abrogated in cells pretreated with ROS inhibitors. Using pharmacological approach we demonstrated that autophagy played a critical role in morphine-induced synaptic impairment and was downstream of both oxidative and ER stress. Intriguingly, exposure of morphine-treated neurons to PDGF-BB resulted in reversal of morphine-mediated loss of spine density. This effect was accompanied by rescue of morphine-mediated loss vGlut1 and a concomitant upregulation of GAD65. We thus conclude that morphine-mediated synaptic impairment involving oxidative stress via NADPH oxidase and the downstream ER stress-autophagy pathways could be restored by PDGF-BB. PDGF could thus be considered as a therapeutic strategy for ameliorating morphine-associated cognitive impairment.

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Poster

575. The Dynamic Synapse

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Topic: B.08. Synaptic Plasticity

Support: NWO

Title: Anxiety elicits synaptic potentiation through activation of AMPA-receptor subunit GluA3

Authors: *M. RENNER, E. H. H. ALBERS, N. GUTIERREZ-CASTELLANOS, N. R. REINDERS, T. R. LODDER, C. I. DE ZEEUW, H. W. KESSELS;
Netherlands Inst. For Neurosci., Amsterdam, Netherlands

Abstract: Emotions influence memory formation. Norepinephrine release during arousal creates vivid memories by facilitating the synaptic delivery of GluA1-containing AMPA-receptors. However, the synaptic mechanisms that explain why high norepinephrine levels fail to improve memory formation during severe anxiety have remained unclear. Here we show that intense fear induces a massive and transient synaptic potentiation in the hippocampus by activating AMPA-receptor subunit GluA3. Under basal conditions GluA3-containing AMPA-receptors are inactive and contribute little to synaptic currents. During anxiety a rise in intracellular cyclic AMP driven by norepinephrine restores GluA3 channel and receptor function, leading to an increase in synapse strength. When mice are in a state in which GluA3-containing AMPA-receptors are activated, the ability to encode contextual fear memories is attenuated. We propose that the activation of GluA3-plasticity during an anxious moment prevents memories from becoming too strong.

Disclosures: **M. Renner:** None. **E.H.H. Albers:** None. **N. Gutierrez-Castellanos:** None. **N.R. Reinders:** None. **T.R. Lodder:** None. **C.I. De Zeeuw:** None. **H.W. Kessels:** None.

Poster

575. The Dynamic Synapse

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Topic: B.08. Synaptic Plasticity

Support: Rutherford Discovery Fellowship to J Reynolds

Neurological Foundation W & B Miller Scholarship to L Boddington

Title: Electrical theta-burst stimulation modulates interhemispheric inhibition after photothrombotic stroke

Authors: *L. J. BODDINGTON, J. P. GRAY, J. N. J. REYNOLDS;
Anat., Univ. of Otago, Dunedin, New Zealand

Abstract: Interhemispheric inhibition (IHI) is thought to be altered after stroke. In anaesthetized rats we found that application of low-intensity electrical stimulation in an intermittent theta-burst stimulation (iTBS) pattern to the motor cortex abolishes interhemispheric inhibition (IHI) onto the opposite motor cortex. In the rat photothrombotic model, we found a month after stroke that iTBS applied similarly to the contralesional motor cortex can improve functional recovery. We hypothesized that this functional recovery was related to the cellular effects of iTBS on IHI. In order to investigate the cellular mechanisms and to explore the potential for using electrical TBS as a stroke therapy, we made *in vivo* intracellular sharp electrode recordings in urethane-anaesthetized rats following stroke and measured IHI in the peri-lesional motor cortex. A photothrombotic stroke was induced in the rat motor cortex, followed by the implantation of a cortical electrode to the contralateral motor cortex one week or four weeks after stroke induction. Rats received either iTBS, continuous TBS (cTBS) or sham stimulation for three weeks after electrode implantation, and following this, measurements of IHI were made from the peri-lesional cortex. In all sham-stimulation treated rats, IHI from the contralesional hemisphere was no different from IHI measured in acute healthy rats. Interestingly, and contrary to our hypothesis, the chronic application of iTBS in either of the delay groups did not reduce IHI compared with sham-stimulated rats (13.0% inhibition iTBS vs 14.1% inhibition sham), however chronic application of cTBS did show a large increase in IHI (23.8% inhibition). Consistent with an enhanced IHI, contralateral cTBS also significantly lowered the excitability of the peri-infarct area as evidenced by the 70% maximal amplitude of the EPSP obtained using a standardized input-output paradigm (4.0 mV ± 2.9 for cTBS, $p<0.05$ compared to other groups, One-Way ANOVA, $F = 4.365$; 12.6 mV ± 6.7 for iTBS and 13.6 mV ± 6.6 for sham, no difference). Tonic alterations in IHI and peri-infarct excitability may explain why the chronic application of electrical cTBS after stroke tends to impair recovery in our rodent model. This however does not fully explain why functional recovery can improve after contralateral application of electrical iTBS. We propose that chronic iTBS may reduce IHI dynamically during motor initiation. Further investigations will determine whether increasing the dose of stimulation increases the effects on IHI and excitability and further modulates functional recovery.

Disclosures: L.J. Boddington: None. **J.P. Gray:** None. **J.N.J. Reynolds:** None.

Poster

575. The Dynamic Synapse

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Support: Carlsberg Foundation

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DFF-Sapere Aude 2014

Lundbeck Foundation

Title: Functional characterization of SNPs in the CPG2 region of human SYNE1 with potential relevance to Bipolar Disorder

Authors: *M. A. RATHJE, S. LOEBRICH, E. NEDIVI;
Picower Inst. for Learning and Memory, MIT, Cambridge, MA

Abstract: Bipolar disorder (BD) is a debilitating neuropsychiatric disease. A large genome-wide association study (GWAS) investigating risk genes for BD identified a significant association in parts of the human SYNE1 gene homologous to the region of rat Syne1 encoding CPG2, a postsynaptic neuronal protein localized to excitatory synapses and an important regulator of glutamate receptor internalization. Deep sequencing of patient and control populations in the human CPG2 locus identified multiple single nucleotide polymorphisms (SNPs) within protein coding and regulatory regions. This suggests that variation in human CPG2 function may affect glutamate receptor cycling in a way that would influence susceptibility to BD. To investigate this, we mapped CPG2 transcripts in the SYNE1 gene and cloned a full-length human CPG2 cDNA. We show this transcript is expressed in human neocortex and hippocampus. Using a lenti-viral gene knock down/replacement strategy and surface receptor internalization assays, we found that human CPG2 localizes to dendritic spines in rat hippocampal neurons and is functionally equivalent to rat CPG2 in regulating glutamate receptor internalization. Using this molecular replacement strategy, we have identified SNPs in exonic regions of the SYNE1 gene that significantly decrease CPG2 function. Elucidating the role of CPG2 in synaptic function may provide important insight to the cellular mechanisms of glutamatergic neurotransmission and its implications for neuropsychiatric diseases such as BD.

Disclosures: **M.A. Rathje:** None. **S. Loebrich:** None. **E. Nedivi:** None.

Poster

575. The Dynamic Synapse

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 575.15/B102

Topic: B.08. Synaptic Plasticity

Support: H. Lundbeck A/S and Takeda Pharmaceutical Company Ltd.

Title: Subchronic vortioxetine increases levels of Arc protein and phosphorylation of S845-GluR1 in the mouse frontal cortex - a putative mechanism underlying its pro-cognitive properties

Authors: P. KUGATHASAN[1], M. GULINELLO[2], C. SÁNCHEZ[1], *Y. LI[1];
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Abstract: Introduction: α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors (AMPA-R) are critical for the regulation of synaptic plasticity (e.g. formation of long-term potentiation [LTP]), which is essential for learning and memory. Activity-regulated cytoskeletal protein (Arc) is an immediate early gene which regulates AMPA-R trafficking via endocytosis of its GluR1 subunit. Several studies indicate that phosphorylation of serine 831 (by protein kinase C and calcium/calmodulin-dependent protein kinase II) and serine 845 (by protein kinase A, PKA) on GluR1 are critical for surface expression of AMPA-R and formation of LTP. The antidepressant vortioxetine (VOR) shows beneficial effects on cognitive function in preclinical and clinical studies. Furthermore, VOR increased LTP in rat hippocampus slices and expression of Arc mRNA in the hippocampus and frontal cortex in mice. Aims: To examine effects of subchronic VOR on protein levels of Arc and GluR1, and phosphorylation of GluR1, at baseline (home cage) and after exposure to a novel environment (novelty, a condition may induce Arc expression). **Methods:** Female C57BL mice were treated for 1 month with VOR-infused or regular chow. The VOR dose targeted full occupancy of serotonin transporters. Brains from mice exposed to a novel environment (for 6 min) were collected after 1h (to allow for protein synthesis) and compared to mice kept in the home cages (n=6 per treatment condition). Arc, GluR1, p-S831-GluR1 and p-S845-GluR1 levels were measured in frontal cortex by western blotting. Results were normalized to glyceraldehyde-3-phosphate dehydrogenase (Arc, GluR1) or GluR1 (p-S845 and p-S831) levels, and expressed as fold changes compared to baseline controls. Novelty and VOR effects were analyzed by 2-way ANOVA followed by Tukey-Kramer t-tests. $p<0.05$ was considered significant. **Results:** VOR significantly increased Arc levels, especially in the group exposed to novelty. Novelty had no effect on Arc protein. Novelty, but not VOR, significantly increased total GluR1 levels. There were overall effects of novelty and VOR on p-S845-GluR1 levels, but post-hoc analysis showed that only VOR increased p-S845-GluR1 at both baseline and novelty conditions. Neither novelty nor VOR affected p-S831-GluR1 levels. **Conclusion:** VOR increased cortical Arc protein, particularly after exposure to novelty, and increased PKA-dependent p-S845-GluR1 levels. These mechanisms may be important for VOR's effects on synaptic plasticity, and possibly also for its beneficial effects on cognitive function.

Disclosures: **P. Kugathasan:** None. **M. Gulinello:** F. Consulting Fees (e.g., advisory boards); Lundbeck Research USA. **C. Sánchez:** A. Employment/Salary (full or part-time):; Lundbeck Research USA. **Y. Li:** A. Employment/Salary (full or part-time):; Lundbeck Research USA.

Poster

576. Oscillations and Synchrony: Unit Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 576.01/B103

Topic: B.09. Network Interactions

Support: NIH P41-EB001978

DARPA N66601-09-C-2081

Title: Functional cannabinoid-induced isolation of CA1 from CA3 in rodent hippocampus

Authors: ***R. SANDLER**[1], D. FETTERHOFF[2], T. BERGER[1], D. SONG[1], R. HAMPSON[2], V. MARMARELIS[1];
[1]USC, Los Angeles, CA; [2]Wake Forest Univ., Winston-Salem, NC

Abstract: Much of the research on cannabinoids (CBs) has focused on the effects they have at the molecular and synaptic level. However, the effects of CBs on the dynamics of entire circuits of neural populations' remains poorly understood, especially given that their effects at the cellular level are often opposing. For example, CBs have been shown to promote independent mechanisms which would both suppress and increase network excitation. Similarly, different studies have shown that CBs have both proconvulsant and anticonvulsant properties on seizures. This study aims to disentangle the effects of CBs on the functional dynamics of hippocampal networks by using data-driven nonparametric modeling. Six rodents were trained to criterion on the Delayed-NonMatch-to-Sample (DNMS) task. Each rodent was subjected to 10 control sessions and 10 sessions exposed to Tetrahydro-cannabinol (THC), the primary cannabinoid found in marijuana. During each session, a multi-electrode array was used to record activity from the CA3 and CA1 regions of the rodent hippocampus. Multivariate autoregressive (MVAR) models describing the dynamical transformation from CA3 to CA1 were estimated from the data Traditional modes of analysis showed THC had no effect on rate coding (MFR) and only a slight effect on temporal coding (theta power). Systems analysis however, showed that THC strongly reduced theta information flow from CA3 to CA1. Furthermore, on a network level, by reducing feedforward excitation and increasing CA1 feedback excitation THC led to a functional isolation of CA1 from CA3. Both of these effects were shown to be correlated with behavioral

impairments in rodents during the DNMS task. This work is to our knowledge the first attempt to use data-driven nonparametric modeling techniques to understand the effects of cannabinoids on neural circuits. Clarifying the effects of THC on the network level may provide insight in how to optimize the use of THC as an anticonvulsant drug.

Disclosures: **R. Sandler:** None. **D. Fetterhoff:** None. **T. Berger:** None. **D. Song:** None. **R. Hampson:** None. **V. Marmarelis:** None.

Poster

576. Oscillations and Synchrony: Unit Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 576.02/B104

Topic: B.09. Network Interactions

Support: Medical Research Council

Wellcome Trust

European Research Council

Title: Online modulation of hippocampal oscillatory activity *in vivo*

Authors: ***D. A. KUZMIN**, E. C. NICHOLSON, M. WESTON, D. M. KULLMANN; Univ. Col. London, London, United Kingdom

Abstract: Network oscillations in the brain are a strong candidate mechanism to modulate the flow of information among anatomically connected regions. Available evidence for this hypothesis is however largely correlational. A direct test would require a tool to manipulate the frequency, amplitude and/or phase of population oscillations without preventing neurons from encoding information in a population rate code. Optogenetics enables temporally precise manipulation of populations of neurons. In order to test its potential use to manipulate on-going oscillations we expressed the red-shifted excitatory opsin C1V1 in hippocampal pyramidal neurons and recorded the local field potential with an optrode positioned in the pyramidal cell layer in CA3 or CA1 in either anaesthetized or awake mice. Feedback control of laser illumination achieved bidirectional modulation of the amplitude of a gamma oscillation elicited by a slowly evolving ramp laser command. Oscillation gamma amplitude could also be modulated when the oscillation arose spontaneously. This ‘oscillation clamp’ may prove versatile in probing the behavioral role of population oscillations, especially in relation to their proposed roles in mediating flexible functional connectivity in the brain.

Disclosures: **D.A. Kuzmin:** None. **E.C. Nicholson:** None. **M. Weston:** None. **D.M. Kullmann:** None.

Poster

576. Oscillations and Synchrony: Unit Studies

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Program#/Poster#: 576.03/B105

Topic: B.09. Network Interactions

Support: Major State Basic Research Program of China (2011CBA00403, X.-h.Z.)

Title: GABAergic interneuron subtypes differentially regulate beta and gamma band oscillatory activity of primary visual cortex in awake mice

Authors: ***G. CHEN**[1], M. J. RASCH[2], Q. YE[2], X. H. ZHANG[2];
[1]Inst. of Neuroscience,Chinese Acad. Of Scien, Shanghai, China; [2]State Key Lab. of Cognitive Neuroscience&Learning, Beijing, China

Abstract: Neuronal population activity in the intact brain often exhibits different rhythmic patterns of distinct frequency ranges (0.01-120 Hz). The neuronal oscillations reflect different brain states and participate in specific sensory functions or behavioral tasks. In the awaking states, the most ubiquitous oscillations are rhythms in the beta (12-35 Hz) and gamma frequency (35-90 Hz) bands. Inhibitory GABAergic interneurons, though constituting 15-20% of the population in the cortex, possess diverse subtypes and play important roles in modulating cortical oscillations. However, how different interneuron subtypes gate the generation of distinct band of oscillations remains elusive. We combined extracellular electrophysiological recording and optogenetic methods to examine the contribution of distinct GABAergic interneuron subtypes, somatostatin (SOM)- and parvalbumin (PV)- expressing interneurons, to rhythmic activities in primary visual cortex of head-fixed awake mice. We found that drifting grating visual stimulus can significantly induce slower beta (15-35Hz) and modulate faster gamma band (50-80Hz) oscillations simultaneously. With the optogenetic tagging, the identified SOM+ interneuron shows an involvement to induced beta but not gamma band oscillatory activity, however, PV+ interneuron possesses two subtypes: one preferentially involves into beta oscillation, and the other involves into both beta and gamma oscillations. Optogenetic silencing or activating one type of interneuron uncovered that SOM+ and PV+ interneuron paces lower (<20Hz) and higher (20-80Hz) frequency band activity respectively. Inactivation of SOM+ interneuron abolished only the visual induced beta oscillation, however, inactivating PV+ interneuron abolished both the visual induced beta and gamma oscillations. Computational modeling results quantitatively

show that beta oscillation is preserved only under balanced activity between SOM+ and PV+ interneurons, meanwhile, visual modulated gamma oscillation can be simulated by the firing change of PV+ interneuron. These results provide evidence that SOM+ and PV+ interneuron subtypes distinctively and synergistically contribute to beta and gamma band activities in primary visual cortex of behaving mice.

Disclosures: G. Chen: None. **M.J. Rasch:** None. **Q. Ye:** None. **X.H. Zhang:** None.

Poster

576. Oscillations and Synchrony: Unit Studies

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Topic: B.09. Network Interactions

Support: Netherlands Organization for Scientific Research (NWO) Excellence Grant for the Brain & Cognition (project 433-09-208)

Fondation Fyssen

Title: Membrane potential dynamics of spontaneous and visually evoked gamma rhythmicity in V1 of awake mice

Authors: *Q. PERRENOUD[1,2], C. M. A. PENNARTZ[2], L. J. GENTET[3];
[1]Dept. of Neurobio., Yale Univ. Sch. of Medecine, New Haven, CT; [2]Univ. of Amsterdam, Amsterdam, Netherlands; [3]Univ. Lyon 1, Lyon, France

Abstract: Cortical gamma rhythmicity (30-80 Hz) is believed to play important functions in neural communication and arises from the activity of parvalbumin-expressing interneurons (PV). However, the mechanisms underlying its emergence and temporal patterning in awake animals are unclear. Here, we characterized the intracellular activity of PVs and pyramidal cells (PYRs) during spontaneous and visually evoked gamma rhythmicity in layers 2/3 of V1 of awake mice using targeted patch-clamp recordings and synchronous local field potentials (LFPs). Strong gamma bouts (1-3 cycles) occurred when PVs and PYRs were depolarizing, entrained their membrane potential rhythmically and emerged from the activity of PVs with characteristics of an Interneuron-Network Gamma model (ING). PV firing phase-locked unconditionally to gamma rhythmicity. However, PYRs only phase-locked to visually evoked gamma oscillations. Taken together our results indicate that gamma rhythmicity is driven by correlated background synaptic activity and synchronizes the output of cortical neurons depending on external sensory drive.

Disclosures: **Q. Perrenoud:** None. **C.M.A. Pennartz:** None. **L.J. Gentet:** None.

Poster

576. Oscillations and Synchrony: Unit Studies

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Topic: B.09. Network Interactions

Support: ERC Advanced Grant 268548

Title: Phase-locked inhibition, but not excitation, underlies hippocampal ripple oscillations in awake mice *in vivo*

Authors: **J. GAN**, S.-M. WENG, A. J. PERNÍA-ANDRADE, J. CSICSVARI, *P. JONAS; IST Austria, Klosterneuburg, Austria

Abstract: Sharp wave-ripple (SWR) events, which occur during awake immobility and non-rapid eye movement sleep, are thought to play a key role in memory consolidation. However, the underlying synaptic mechanisms *in vivo* remain controversial (English et al. 2014, J Neurosci 34:16509; Maier et al. 2011, Neuron 72:137). We performed simultaneous whole-cell patch-clamp recordings from CA1 pyramidal neurons and extracellular local field potential (LFP) measurements in awake mice *in vivo*. Recordings were obtained after full recovery from initial anesthesia and habituation to the head-restraint configuration. During resting wakefulness, SWRs occurred with a mean frequency of 0.22±0.02 Hz (153 events in 6 mice). On average, SWR events had a duration of 55.2±1.8 ms, and contained 8.6±0.3 ripple cycles, generated at a frequency of 153.2±2.0 Hz. To examine the synaptic mechanisms of SWRs, we measured excitatory and inhibitory synaptic currents (EPSCs and IPSCs) in CA1 pyramidal neurons during SWRs *in vivo* under voltage-clamp conditions at -70 mV and +10 mV, respectively (series resistance 16±2 MΩ). SWR-associated peak conductance was 1.6±0.3 nS for excitation and 3.5±0.7 nS for inhibition, corresponding to an inhibition-to-excitation conductance ratio of 3.7±1.0. Thus, synaptic inhibition dominated over excitation. Furthermore, plotting EPSC and IPSC peak amplitude against SWR amplitude revealed a significant correlation for IPSCs, but not for EPSCs. Thus, the magnitude of inhibition, but not that of excitation, predicted the amplitude of SWRs. To evaluate the phase relation between synaptic currents and ripple oscillations *in vivo*, we performed slope analysis of synaptic currents (Maier et al. 2011, Neuron 72:137). Onsets of EPSCs and IPSCs were detected as the 1-25% steepest downward and upward slopes, respectively, in the synaptic current traces (1517 and 1305 events). The Hilbert transform of filtered LFP traces (100-250 Hz band pass) was computed, and onsets of EPSCs and IPSCs

were individually assigned to phase values. Whereas EPSCs were uniformly distributed (P=0.79), IPSCs were significantly clustered in the ascending phase of ripple cycles (P=0.02; phase angle: -26.2±39.4º). Thus, phasic inhibition, but not excitation, was phase-locked to individual ripple cycles. Consistent with these results, slope-triggered averages of the LFP were rhythmically modulated for upward slopes (i.e. IPSC onsets), but not for downward slopes (i.e. EPSC onsets). In conclusion, our results indicate that inhibition dominates over excitation during SWRs, and phasic inhibition, but not excitation, shapes ripple oscillations in the hippocampal CA1 region *in vivo*.

Disclosures: J. Gan: None. **S. Weng:** None. **A.J. Pernía-Andrade:** None. **J. Csicsvari:** None. **P. Jonas:** None.

Poster

576. Oscillations and Synchrony: Unit Studies

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: B.09. Network Interactions

Support: CAPES/STINT

Kjell och Märta Beijers Foundation

Title: Martinotti cells defined by Chrna2 coordinate layer V pyramidal cell activity

Authors: *M. M. HILSCHER[1,2], R. N. LEÃO[1,2], K. E. LEÃO[2], K. KULLANDER[1]; [1]Dept. of Neurosci., Uppsala Univ., Uppsala, Sweden; [2]Brain Inst., Federal Univ. of Rio Grande do Norte, Natal, Brazil

Abstract: GABAergic interneurons in the mammalian cortex possess a broad variety of morphological, neurochemical and electrophysiological properties. The somatostatin+ Martinotti cells (MCs), are the most prominent slow-inhibitory interneurons targeting distal dendrites of pyramidal cells (PCs). We identified the cholinergic nicotinic receptor alpha2 (Chrna2) as a marker to label layer V/VI MCs ($MCs^{\alpha2}$). We used a Chrna2-cre mouse line crossed with a fluorescent reporter (tdTomato) confirming that the layer V/VI $MCs^{\alpha2}$ exhibit the defining characteristic of a long axonal projection to layer I and extensive ramifications in layer IV. Immunohistochemistry showed that the vast majority of Tomato+ cells comprised a subpopulation of somatostatin+ interneurons. Whole-cell current- and voltage-clamp recordings were performed in the auditory cortex and confirmed that passive and active electrophysiological

properties of $MC^{\alpha 2}$ resemble the classical low-threshold spiking patterns of MCs. Recorded $MC^{\alpha 2}$ usually exhibited spike frequency adaptation and burst discharge when depolarized from hyperpolarized potentials. In paired recordings, layer V PCs showed long inhibitory postsynaptic potential rise times and synaptic depression upon electrical stimulation of the presynaptic $MC^{\alpha 2}$. Moreover, optogenetic manipulation of channelrhodopsin-activated $MCs^{\alpha 2}$ demonstrated that layer V PC spiking can be controlled by MCs^{α} via oscillatory inhibition of PC distal dendrites suggesting that MCs^{α} may play a key role for PC network coordination.

Disclosures: **M.M. Hilscher:** None. **R.N. Leão:** None. **K.E. Leão:** None. **K. Kullander:** None.

Poster

576. Oscillations and Synchrony: Unit Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 576.07/B109

Topic: B.09. Network Interactions

Title: Criticality is non-stationary in cortical neuronal networks

Authors: ***G. HAHN**[1], A. PONCE-ALVAREZ[1], C. MONIER[2], G. BENVENUTI[3], A. KUMAR[4], F. CHAVANE[3], G. DECO[1], Y. FRÉGNAC[2];
[1]Univ. Pompeu Fabra, Barcelona, Spain; [2]UNIC/CNRS, Gif-sur-Yvette, France; [3]INT, Marseille, France; [4]KTH, Stockholm, Sweden

Abstract: The brain is able to generate complex spatiotemporal activity patterns which endow cortical networks with the ability to process and store information about the environment. Recent theoretical and experimental studies proposed the theory of criticality as a potential mechanism for complex dynamics in neuronal networks. Signatures of critical systems such as power laws and long-range spatio-temporal correlations were found both in local field potentials (LFP) and spiking activity of *in vitro* and *in vivo* preparations and interpreted as the presence of critical neural dynamics. Here, we recorded spontaneous activity in the primary visual cortex of anesthetized cats and awake monkeys using different types of multi-electrode arrays, and studied critical features of spiking activity as a function of cortical state. We separated up to five different states with different levels of population synchronization in spiking activity which in the case of the monkey were correlated with the level of arousal. Assessment of criticality based on neuronal avalanche analysis revealed a strong dependence of avalanche distributions on cortical state with power laws only to be found in highly synchronized states. In contrast, markedly curved distributions were observed during desynchronized states. Moreover, we investigated the presence of criticality by using maximum entropy models to study the joint

spiking activity patterns during the different cortical states. This allowed us to extract relevant "thermodynamic" features of the ensemble activity, such as the heat capacity that characterizes the dispersion of energies attributed to the activity patterns. The analysis of heat capacity also shows significant state-dependence and confirms that synchronized states are closer to criticality than desynchronized states. Overall, our results indicate that critical features of spiking activity strongly depend on the cortical state and are non-stationary.

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Poster

576. Oscillations and Synchrony: Unit Studies

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Topic: B.09. Network Interactions

Support: NIMH 1P50MH094271

Nancy Lurie Marks Foundation

SFARI

RettSyndrome.org

Title: Dissecting parvalbumin-cell receptor mechanisms underlying ketamine action

Authors: N. PICARD[1], *H. H. LEE[2], A. E. TAKESIAN[3], M. FAGIOLINI[3], T. K. HENSCH[3]; [2]Neurol., [1]Boston Children's Hosp., Boston, MA; [3]Boston Children's Hosp., boston, MA

Abstract: Ketamine is known to decrease cortical inhibition in humans and behaving animals, leading to cognitive deficits such as psychosis. The mechanisms underlying this ketamine action are far from understood but evidence points toward an effect mediated through fast spiking Parvalbumin (PV)-positive inhibitory interneurons. Here, we used genetic manipulations to selectively remove receptors from PV cells, to further understand the effect of a low dose of ketamine (8mg/kg) on cortical activity in mice. In anesthetized wild-type (WT) animals, single-unit recordings in visual cortex showed that a single ketamine injection rapidly increased both spontaneous activity and visually-evoked responses of pyramidal cells. As ketamine is a NMDA receptor antagonist, we first deleted the NMDA receptor 2A subunit specifically from PV cells by crossing PV-Cre mice with Floxed GluN2A mice. In these animals, the ketamine-induced

increase in pyramidal cell activity was delayed, but eventually reached control levels 60 minutes after the injection. This result fully explained a similar loss of the initial ketamine response in global NMDA-2A receptor knockout mice. Strikingly, whole-cell recordings *in vitro* revealed a broadening of PV-to-PV inhibitory postsynaptic currents (IPSC) in the presence of ketamine (McNally et al, 2011). To investigate the involvement of GABAergic inhibition in the ketamine response, we also recorded mice in which the GABAAR-alpha1 subunit was selectively removed from PV cells to mimic this IPSC broadening. In these mutants, ketamine now produced an opposite effect to that seen in WT, rapidly decreasing the firing rate of pyramidal cells. Importantly, NMDA receptor subunits were unaltered in PV-cells from these mice. At a system level, the electroencephalogram of awake WT mice exhibited an increase in frontal cortex gamma oscillations in response to low-dose ketamine. This effect was smaller in the PV-Cre:GABAAR-alpha1 knockout mice and enhanced in the PVCre:NMDA-2A mutants. Taken together, our results demonstrate that the excitatory/inhibitory balance within PV cells is essential for determining the response to low-dose ketamine

Disclosures: **N. Picard:** None. **H.H. Lee:** None. **A.E. Takesian:** None. **M. Fagiolini:** None. **T.K. Hensch:** None.

Poster

576. Oscillations and Synchrony: Unit Studies

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 576.09/B111

Topic: B.09. Network Interactions

Support: HHMI

Title: Cell-type specific microcircuitry in the CA3 region of the hippocampus

Authors: *D. L. HUNT, N. SPRUSTON;
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Abstract: Cell-types and microcircuits have been canonically defined based on cellular morphology, physiology, and afferent/efferent projection patterns. While these criteria remain indispensible, the classical techniques used to establish these standards often lack the specificity necessary to dissect the complexity of intermixed but distinct pathways. Modern techniques utilizing transgenic mice and optogenetics have the ability to interrogate microcircuits with cell-type specificity, redefining our understanding of circuit architecture and function. Here we have identified at least two types of principal cells within the CA3 region of the murine hippocampus.

These two pyramidal cell-types have distinct morphological attributes, physiological properties, and connection specificity. By combining optogenetics and electrophysiology with high-resolution semi-automated neuronal reconstruction, we demonstrate distinct signatures of cell-type specific microcircuits in the CA3 region. One sub-population of CA3 principal neurons lack the characteristic thorny excrescences typically associated with canonical CA3 pyramids. These athorny pyramidal cells also have other distinct morphological features such as fewer dendritic branches, lower branch order, and decreased dendritic diameter compared to their thorny counterparts. Athorny neurons also exhibited bursting intrinsic firing patterns, higher input resistance and a more prominent post-spike afterdepolarization. Most strikingly, we utilized channelrhodopsin assisted circuit mapping and were unable to find any evidence that athorny cells receive direct mossy fiber input; however they do receive di-synaptic recurrent input from other CA3 cells. Together, these data suggest that this subpopulation of athorny bursting cells constitute a previously unrecognized feed-forward sub-layer embedded within the CA3 recurrent network.

Disclosures: **D.L. Hunt:** None. **N. Spruston:** None.

Poster

576. Oscillations and Synchrony: Unit Studies

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Topic: B.09. Network Interactions

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Strategic Research Programme in Diabetes at Karolinska Institutet

Internal funds from Karolinska Institutet

Title: Electrical connectivity overrides individual neuron dynamics dictating homogenous network behavior

Authors: *A. S. STAGKOURAKIS, C. THÖRN PEREZ, A. HELLYSAZ, R. AMMARI, C. BROBERGER;
Neurosci., Karolinska Institutet, Stockholm, Sweden

Abstract: Rat tuberoinfundibular dopamine (TIDA) neurons exhibit robust synchronized low-frequency oscillations *in vitro*, providing a tractable mammalian system for the study of spontaneous network rhythms. While the TIDA oscillation appears to depend on intact gap junction coupling between neurons, the nature of electrical coupling and its contribution to network behaviour remains to be addressed. Here, we exploited an unexpected species difference to explore this issue. Whole-cell recordings were performed in male rat and mouse (P21-30) hypothalamic slices maintained in oxygenated artificial cerebrospinal fluid at near physiological temperature (ca. 34oC) under differential interference contrast visualization. While rat TIDA cells oscillated in robust synchrony and phase alignment, mouse TIDA neurons were found to exhibit rhythmic but uncoordinated oscillatory discharge. Mouse TIDA oscillations were of higher frequency (mouse: 0.4±0.05Hz, n=78; rat: 0.15±0.01Hz, n=85) and less regular and mouse TIDA neurons were more depolarized (oscillation nadir mouse: -51.1±0.9mV; rat: -66±1.1mV). Notably, whereas rhythmicity persists at constant frequency in rat TIDA cells upon progressive hyperpolarization via negative current injection, this manipulation causes the oscillation to collapse in the mouse (ca. -80mV, n=34). We next addressed if differences in electrical characteristics or connectivity might explain the discrepant network behaviour. Baseline membrane properties - as assessed by square pulse commands in current and voltage clamp - were not obviously different between the two species, and in both cases phasic discharge endures when fast synaptic transmission is blocked. However, substantial electrical connectivity was found in rat (n=32/64 pairs; 0.18±0.02 coupling coefficient), but was absent in mouse (n=0/40 pairs) TIDA neurons. These findings suggest that the presence of gap junctions not only synchronizes neurons but also determines network frequency. Investigation of the preferred frequency of individual TIDA neurons provided further support to this conclusion: while the cells in both species exhibit maximum impedance at the same frequency, this frequency in the mouse (n=18, 0.35±0.03Hz) is the same as oscillation frequency, whereas the rat oscillation frequency is significantly lower than the average preferred frequency of individual cells (n=31, 0.30±0.02Hz).

Disclosures: **A.S. Stagkourakis:** None. **C. Thörn Perez:** None. **A. Hellysaz:** None. **R. Ammari:** None. **C. Broberger:** None.

Poster

576. Oscillations and Synchrony: Unit Studies

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Program#/Poster#: 576.11/C1

Topic: F.02. Animal Cognition and Behavior

Support: ONR-YIP 26-1302-8750

Title: Dynamical constraints on improving coding fidelity through the `sign rule'

Authors: *B. KRIENER, I. FIETE;
Ctr. for Learning and Memory, Univ. of Texas at Austin, Austin, TX

Abstract: It has been suggested that noise correlations, appropriately tuned, can substantially increase coding fidelity in neural representations compared to if noise is independent across neurons. For stimulus discrimination, correlations that decrease noise fluctuations along the stimulus-response direction improve information transfer compared to the uncorrelated case [1-3]. This observation is called the `sign ruleâ€™ in two dimensions, because noise correlations are of opposite sign from the stimulus-evoked (signal) correlations. Finally, large gains in coding capacity can result from realistically small microscopic correlations, if of the right variety [3]. We ask whether it is plausible to independently tune signal and noise correlations according to the sign rule, considering that in reality both are shaped by the recurrent network dynamics. We investigate simple models of neural networks in quasi-2D configurations, in which we derive the signal and noise correlations as a function of network parameters, including weights, for both stationary and time-dependent stimuli. In linear networks, optimizing weights to flatten noise along the stimulus direction results in vanishing signal-to-noise ratio (SNR), while maximizing the time-varying stimulus-content in the response yields finite fluctuation size along the stimulus direction that is independent of network parameters and can thus not be further minimized. We extend our analysis to balanced random networks of binary and leaky integrate-and-fire neurons. These networks can assume asynchronous-irregular activity states akin to what is observed in cortex, and pairwise correlations are inherently decreased by the ongoing recurrent inhibitory feedback [4]. Though this helps to reduce noise correlations, it also limits the achievable amount of stimulus content in the network response. We conclude that the form of correlation shaping required for the sign rule also modifies the stimulus response to the detriment of the SNR, at least in our network architectures. [1] Abbott & Dayan, 1999 [2] Averbeck et al., 2006 [3] da Silveira & Berry, 2013; Hu et al., 2014 [4] Renart et al., 2010; Tetzlaff et al., 2013; Helias et al., 2014

Disclosures: **B. Kriener:** None. **I. Fiete:** None.

Poster

577. Modulation of Neuronal Firing Properties I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 577.01/C2

Topic: B.10. Intrinsic Membrane Properties

Title: NMDA receptor and protein kinase A signaling modulates firing properties of cerebellar stellate cells

Authors: *R. ALEXANDER[1,2], D. BOWIE[3];
[2]Integrated Program in Neurosci., [3]Pharmacol. and Therapeut., [1]McGill Univ., Montreal, QC, Canada

Abstract: In the mammalian brain, the action potential (AP) underlies the complex, oscillatory behavior of neuronal circuits orchestrated by a network of fast-spiking inhibitory interneurons and slower-spiking excitatory principal neurons. In the cerebellum, a region classically associated with motor coordination and learning, the stellate cell is one of several subtypes of GABAergic inhibitory interneurons found in the cerebellar cortex. We have observed a novel form of NMDA receptor-dependent firing rate modulation that increases the degree of inhibition on the cerebellar micro-circuit. Acute slices of cerebellar vermis were obtained from both male and female wild-type C57BL/6 mice by vibrating-blade microtome sectioning. Slices were continually perfused with saline solution and visually identified using an upright microscope. After establishing whole-cell configuration during patch-clamp recording, these cells exhibit a passive increase in AP frequency evoked by current steps over the course of recording (3.46 fold after 25 minutes), curiously also observed in excitatory granule cells but not Purkinje neurons. This increase in firing rate was found to be related to a hyperpolarization of AP activation threshold (-8.2 mV change, n=6 stellate cells), which allowed cells to spike earlier and more often. Performing cell-attached electrophysiological recordings with Na+-based pipette solution yielded no increase in spontaneous action current frequency, but after local application of NMDA agonist (1 mM) there was a chronic increase in number of spikes (56%, n=5 stellate cells) that closely mirrored the time course observed in whole-cell experiments. Repeating cell-attached recordings with high K+ internal pipette solution induced a similar chronic increase in spontaneous action currents but could be blocked by bath application of NMDA receptor antagonist D-APV (10 μM), suggesting this firing rate plasticity mechanism is effected by NMDA receptor signaling. Furthermore, inhibiting the activity of protein kinase A (5 μM PKI-(6-22)-amide), but not protein kinase C (1 μM Gö 6983), significantly attenuated the hyperpolarization of AP activation threshold over the whole-cell recording duration. Further investigation into the signaling cascade responsible for this firing rate increase has physiological relevance as a novel regulatory mechanism of inhibitory circuits. Our work will provide new insight into the role of NMDA receptor-dependent excitability modulation in the cerebellar circuit.

Disclosures: R. Alexander: None. **D. Bowie:** None.

Poster

577. Modulation of Neuronal Firing Properties I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 577.02/C3

Topic: B.10. Intrinsic Membrane Properties

Support: Fondecyt Grant 1141170

Anillo Grant ACT-1109

Title: Excitatory and inhibitory innervation of *in vivo* recorded and labeled individual dopaminergic neurons of the ventral tegmental area

Authors: *T. MONTERO, C. GONZALEZ-CABRERA, P. HENNY;
Lab. de Neuroanatomia, Dept. de Anatomia Normal, Pontificia Univ. Catolica De Chile, Santiago, Chile

Abstract: Dopaminergic neurons of the ventral tegmental area (VTA) are involved in several functions such as behavioural reinforcement and motivation. The activity of VTA dopaminergic neurons is controlled by intrinsic membrane properties, which underlie tonic firing, and the activity of glutamatergic, cholinergic and GABAergic afferents, which mostly underlie phasic discharge and/or inhibition. While it is recognised that the distribution of synaptic afferents onto the somatodendritic domain affect the discharge patterns and responses of central neurons, it is yet unknown how the localisation of inputs can affect activity in VTA dopaminergic neurons. In fact, in rat SNc dopaminergic neurons it has been shown that the distribution of GABAergic inputs onto distal dendrites relates to the strength by which neurons respond to noxious stimulation (Henny et al., Nat. Neurosci., 2012). In order to understand the mechanisms that underlie driven activity in VTA dopaminergic neurons, we set up a project to study the somatodendritic distribution of glutamatergic and GABAergic synapses onto individual. In urethane anaesthetised adult mice, we recorded and labeled VTA single neurons using the juxtacellular technique, followed by brain fixation and histological processing. Dopaminergic phenotype of individual neurobiotin-labeled neurons was established by their immuno-positivity to tyrosine hydroxylase (TH). The presence of glutamatergic and GABAergic synaptic inputs onto neurobiotin labeled soma or dendrites, was determined using double labelling for the scaffolding protein homer1 (HOM) or gephyrin (GEPH), as markers of excitatory or inhibitory postsynaptic densities, respectively. The entire somatodendritic domain of neurons was observed and acquired using confocal microscopy, after which we used stereological tools to count and examine the distribution of synaptic inputs.

Disclosures: **T. Montero:** None. **C. Gonzalez-Cabrera:** None. **P. Henny:** None.

Poster

577. Modulation of Neuronal Firing Properties I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 577.03/C4

Topic: B.10. Intrinsic Membrane Properties

Support: EMBO

SNF

Title: Physiology and ion channel expression of axons of amygdala projection neurons

Authors: *J. GRUNDEMANN[1], S. KRABBE[1], E. VOGEL[1], K. BYLUND[1], C. MÜLLER[1], V. SENN[2], A. LUTHI[1];
[1]Friedrich Miescher Inst., Basel, Switzerland; [2]Ernst Struengmann Inst., Frankfurt / Main, Germany

Abstract: Axons are the principal elements of neuronal signal generation and propagation in the brain. Despite this central function, our knowledge of axonal physiology originates mainly from classical studies of peripheral and cranial nerves, which is typically generalized to the CNS. However, there is a growing body of evidence demonstrating that CNS axons are highly diverse between various brain areas with remarkable functional properties that influence neuronal output and signal transmission (Debanne et al., 2011). Most of these studies were performed in the cortex, hippocampus, cerebellum or auditory brain stem, whereas little is known about the physiological function of axons of amygdala projection neurons - pyramidal-like neurons which are critically involved in emotional learning and processing. Here we use a combination of direct axonal electrophysiological recordings and two-photon Ca2+ imaging to characterize the features of axonal action potential initiation, transmission and activity-dependent Ca2+ signaling in basolateral amygdala projection neurons. In addition, we investigated their axonal ion channel distribution and myelination pattern using immunohistochemistry and confocal imaging. These data will not only increase the knowledge of the physiological variety of CNS axon function, but also provide further insight into the functional properties of amygdala projection neurons, which are potential drug targets for the treatment of anxiety disorders. Debanne et al.; Axon physiology; 2011; Physiol Rev.; 91(2): 555-602

Disclosures: J. Grundemann: None. **S. Krabbe:** None. **E. Vogel:** None. **K. Bylund:** None. **C. Müller:** None. **V. Senn:** None. **A. Luthi:** None.

Poster

577. Modulation of Neuronal Firing Properties I

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 577.04/C5

Topic: B.10. Intrinsic Membrane Properties

Support: AHA Grant #13SDG16990083

Title: Investigating action potential initiation and propagation with dynamic clamp: sensitivity to parameters

Authors: *M. A. NAVARRO[1], S. L. DEBS[2], B. R. BERIGAN[1], T. G. CARRON[1], A. M. WOOD[3], L. S. MILESCU[1];
[1]Biol. Sci., Univ. of Missouri, Columbia, MO; [2]Whitman Col., Walla Walla, WA; [3]Washington State Univ., Pullman, WA

Abstract: In mammalian central neurons, action potentials are initiated in the axon initial segment (AIS) by Nav1.2 and Nav1.6 channels, and shaped and terminated by other voltage-gated ion channels. From the AIS, the AP travels down the axon towards the presynaptic site, but also back-propagates towards the soma. The role of axonal sodium channels in AP initiation and propagation is still incompletely understood, mostly because it is difficult to record from these channels at the AIS. Instead, most experimental evidence of axonal activity is obtained indirectly, from electrical recordings at the soma. We have previously developed a real-time computational procedure where a compartmental model of the axon is coupled to a live neuron using dynamic clamp. Here, we are investigating how the observed neuronal behavior, particularly the shape of the AP recorded at the soma, depends on the parameters of the axonal model, such as density and distribution of Nav channels.

Disclosures: **M.A. Navarro:** None. **S.L. Debs:** None. **B.R. Berigan:** None. **T.G. Carron:** None. **A.M. Wood:** None. **L.S. Milescu:** None.

Poster

577. Modulation of Neuronal Firing Properties I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 577.05/C6

Topic: B.10. Intrinsic Membrane Properties

Support: NIA Grant

Title: Neurons in rat retrosplenial cortex display heterogeneity of firing type

Authors: *A. N. NYE[1], C. SONG[1], J. R. MOYER, Jr.[1,2];
[1]Psychology, [2]Biol. Sci., Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: The retrosplenial cortex is a structure that is connected with many different regions of the brain (hippocampus, parahippocampal regions, visual cortex, thalamic nuclei and rhinal cortices) in both primates and rodents. Furthermore, previous human and animal research suggests that the retrosplenial cortex plays a vital role in the learning and memory of spatial and contextual information. Recent data suggests that retrosplenial cortex is also involved in extinction of trace fear conditioning. Unfortunately, few studies have investigated the electrophysiological properties of retrosplenial cortical neurons. In the current study, coronal brain slices were prepared from experimentally naïve adult F344, and Sprague Dawley rats. An upright microscope equipped with infrared DIC optics was used for visualizing the neuron and patch electrode, and whole-cell recordings were made from neurons located throughout different layers of granular retrosplenial cortex. Electrodes included biocytin in order to confirm laminar location of neurons, and obtain detailed morphological analyses. Preliminary analyses of data from 28 neurons revealed several distinct firing patterns, which included regular spiking, late spiking, burst spiking, and double spiking neurons. Regular spiking neurons fired single action potentials at threshold. In contrast burst spiking neurons fired a burst of 3 or more action potentials, and double spiking neurons fired a doublet at threshold. Furthermore, a subset of neurons also displayed a pronounced afterdepolarization, but with higher current injections these neurons also fired a doublet. In response to a just-suprathreshold current injection, late spiking neurons delayed their firing until near the end of the .5-sec current injection (mean spike latency ~629 ms), as compared to neurons from all other firing types (mean spike latency 336 ms). These late spiking neurons also had a more hyperpolarized resting membrane potential (-70 mV versus -64 mV for other cell types) and a higher input resistance (355 MΩ vs. 150 MΩ for other firing types). Ongoing analyses are investigating the relationship between neuronal firing properties and morphological characteristics. These studies will contribute important physiological and morphological data and lay the foundation for understanding how retrosplenial cortex contributes to learning and memory as well as aging-related learning deficits.

Disclosures: **A.N. Nye:** None. **C. Song:** None. **J.R. Moyer:** None.

Poster

577. Modulation of Neuronal Firing Properties I

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Program#/Poster#: 577.06/C7

Topic: B.10. Intrinsic Membrane Properties

Support: Charles A King Trust

NIH P01 NS079419-2

Marie Curie COFUND

Title: Reconciling neuromodulation and homeostasis

Authors: *T. O'LEARY[1], G. DRION[1], A. FRANCI[2], E. MARDER[1];
[1]Volen Ctr. For Complex Systems, Brandeis Univ., Waltham, MA; [2]Mathematics Dept., Univ. Nacional Autónoma de México, Mexico City, Mexico

Abstract: Neuromodulators can alter the activity state of neurons and circuits for prolonged periods. For example, during locomotion, motor circuits switch from one rhythmic state to another, or from quiescence to sustained pacemaking activity [1]. This continual switching poses a potential problem for so-called homeostatic mechanisms, which are traditionally believed to push activity levels toward a 'set point'. Here we show, using a very simple theoretical model of activity-dependent ion channel regulation [2], how pronounced and long-lived changes in activity can be induced by the action of neuromodulators without interfering with ongoing homeostatic regulation. We use physiologically relevant conductance -based models of central pattern generating neurons to illustrate the general theoretical principles. Furthermore, our results reconcile reliable modulation with underlying variability in the ion channels and receptors that are targeted by modulatory substances [3], and offer a clue as to why single modulator receptors sometimes target multiple currents in a neuron. References 1. Marder, E., O'Leary, T., and Shruti, S. (2014). Neuromodulation of circuits with variable parameters: single neurons and small circuits reveal principles of state-dependent and robust neuromodulation. Annual Review of Neuroscience 37, 329-346. 2. O'Leary, T., Williams, A.H., Franci, A., and Marder, E. (2014). Cell types, network homeostasis, and pathological compensation from a biologically plausible ion channel expression model. Neuron 82, 809-821. 3. Marder, E., and Goaillard, J.M. (2006). Variability, compensation and homeostasis in neuron and network function. Nature Rev Neurosci. 7, 563-574.

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Poster

577. Modulation of Neuronal Firing Properties I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: B.10. Intrinsic Membrane Properties

Support: CNRS

Université de Bordeaux

Title: Dopamine modulation of motor cortical microcircuit

Authors: ***M. LE BON-JEGO**, A. MOHANRAJ, A. TAUPIGNON, J. BAUFRETON;
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Abstract: Voluntary movement is mainly a cortical activity and sub-cortical loops including the basal ganglia network are involved in the control of this voluntary movement. Parkinson's disease (PD) is characterized by a progressive degeneration of dopaminergic neurons in the substantia nigra, one of the structures of the basal ganglia. The resulting lack of dopamine is the cause of the typical symptoms observed in this disease characterized by rigidity, resting tremor and akynesia. To better understand what are the cellular and subcellular mechanisms of Parkinson’s disease, most people are focusing on the basal ganglia. However, it has already been shown that 1) the deep layers of the primary motor cortex (M1) received dopaminergic innervation and 2) *in vivo* the activity of neurons in M1 is altered in monkeys rendered parkinsonian. Indeed, neurons exhibiting tonic activity in normal condition switch to bursts of discharge which are synchronized among neurons. Thus, it possible that the dopaminergic innervation of the cortex can be crucial for the operation of this motor cortical microcircuit and consequently the lack of dopamine in PD may impact directly the activity of the cortical microcircuit. The aim of this work is to decipher the role of dopamine on the function of these motor cortical microcircuits in physiological and physiopathological conditions in mice. We use an experimental approach that combines *in vitro* conventional electrophysiology techniques (patch clamp in current or voltage clamp configuration), optogenetic and functional calcium imaging on acute brain slices of PVCreAi9T mice which have all Parvalbumin (PV) inhibitory interneuron fluorescent that allow to discriminate easily between PV IN and pyramidal neuron. We are currently testing the effect of dopamine 1) on the intrinsic properties of the different types of neurons, and 2) on the synaptic transmission between the different elements of the cortical microcircuit. Our results show that in normal condition, dopamine increases the excitability of most type of neurons through a D2 receptor-mediated effect.

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Poster

577. Modulation of Neuronal Firing Properties I

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Topic: B.10. Intrinsic Membrane Properties

Support: Neurodevnet Operating Funds

CIHR Post-doctoral Fellowship

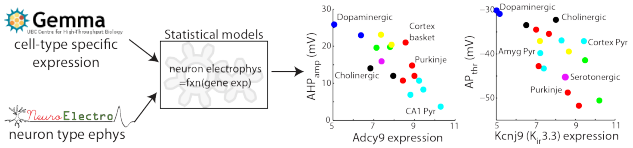
NIH Grant GM076990

Title: Linking the electrophysiological diversity of mammalian neurons to gene expression

Authors: ***S. TRIPATHY**, L. TOKER, D. TEBAYKIN, O. MARCARCI, P. PAVLIDIS; Ctr. for High-throughput Biol., Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Brains achieve efficient function through implementing a division of labor, in which different neurons serve distinct computational roles. Neuronal computations are established through the expression of combinations of ion channels and associated proteins which define neuronal electrophysiological properties. Despite numerous studies characterizing neuronal physiological properties and gene expression patterns, linking neuron genomics to neuron function has been challenging due to the complexity of these heterogeneous data. Here, employing data integration and machine-learning approaches, we combine published reports of neuronal physiological properties with corresponding gene expression measurements. Specifically, we integrate NeuroElectro (www.neuroelectro.org), our database of literature-mined neuron-type physiological diversity, with public genome-wide microarray datasets from purified neuron types (e.g., Dougherty et al. 2008). Thus for 25-30 neuron types, like neocortical basket cells or striatum medium spiny neurons, we can correlate biophysical differences among these neurons with differential expression of specific genes or sets of genes. We demonstrate that relative differences among the genes that neurons express are significantly predictive of neuronal biophysical parameters (such as resting potential and input resistance; R2 = .65, .41). Our approach allows us to ask which genes, of the 20,000 in the genome, are most predictive of electrophysiological diversity. In addition to ion channel genes (such as BK channels, e.g. Kcnma and Kcnmb4), genes related to synaptic plasticity and neuronal differentiation (e.g.

Homer1 and Slit3) were also surprisingly correlated with neuronal physiology. Moreover, cross-referencing these gene lists with those implicated in mental disorders, we find that these genes are also disrupted in epilepsy, schizophrenia, and autism.



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Poster

577. Modulation of Neuronal Firing Properties I

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Topic: B.10. Intrinsic Membrane Properties

Support: NIH Grant MH46742

Marie-Curie COFUND

Title: Paradoxical effects of A-type potassium currents on neuron FI curves

Authors: ***G. DRION**, T. O'LEARY, E. MARDER;
Brandeis Univ., Waltham, MA

Abstract: Neural circuit function can be understood by viewing neurons as input-output devices, each with a characteristic curve describing how synaptic input is transformed into firing frequency. The shape of such a frequency-input (FI) curve is readily measured experimentally and is often characterized into two types of excitable behavior: Type I neurons, which smoothly transition from quiescence to firing at arbitrarily low frequencies as input increases, and Type II neurons, which exhibit a sharp jump to a non-zero frequency at threshold (Hodgkin, 1948; Rinzel and Ermentrout, 1989). Here we revisit the classic result that A-type potassium current (IA) 'linearizes' FI curves, transforming them from Type II to Type I (Connor and Stevens, 1971; Connor et al., 1977; Rush and Rinzel, 1995). Using recently developed analytical tools, we show that the classical account is incomplete: IA causes a second transition from Type I back to a Type II-like FI curve as its density increases. Furthermore, we show that completely unrelated currents, such as calcium currents, can cause the same transitions and that some IA currents

described in the literature cause paradoxical effects. These findings generalize across many neuron models that are found in the literature, regardless of the variety of voltage-gated conductances. References Connor JA, Stevens CF (1971) Prediction of repetitive firing behavior from voltage clamp data on an isolated neurone somata. J Physiol. 213:31-53. Connor JA, Walter D, McKnown R (1977) Neural repetitive firing: modifications of the Hodgkin-Huxley axon suggested by experimental results from crustacean neurons. Biophys J. 18:81-102. Hodgkin AL (1948) The local electric changes associated with repetitive action in a non-medulated axon. J Physiol. 107:165-81 Rinzel J and Ermentrout B (1989) Analysis of neural excitability and oscillations, In ``Methods in Neuronal Modelling: From synapses to Networks", C. Koch and I. Segev, eds. 1989, MIT Press (revised 1998). Rush ME and Rinzel J (1995) The potassium A-current, low firing rates and rebound excitation in Hodgkin-Huxley models. Bull Math Biol. 57:899-929.

Disclosures: **G. Drion:** None. **T. O'Leary:** None. **E. Marder:** None.

Poster

577. Modulation of Neuronal Firing Properties I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 577.10/C11

Topic: B.10. Intrinsic Membrane Properties

Support: NIH 5R21NS082680-02

Title: The depolarized after-potential following the spike in unmyelinated axons in the CNS reduces conduction failures occurring at fever-like temperatures

Authors: D. PEKALA[1], H. SZKUDLAREK[2], *M. RAASTAD[1];
[1]Dept Physiol, Emory Univ. Sch. of Med., Atlanta, GA; [2]Jagiellonian Univ., Krakow, Poland

Abstract: Most axons propagate action potentials (APs) with great fidelity at normal body temperature. However, conduction failures have been detected e.g. in demyelinated axons at fever-like temperatures. Whether such temperatures give failures in the very thin unmyelinated axons typical for cortex is not known. Therefore, we have investigated the influence of temperatures in the upper physiological range on AP propagation in cerebellar parallel fibers (PFs). We used cerebellar slices from 10 - 25 days old rats. Fast synaptic transmission was blocked by adding APV, DNQX and picrotoxin to standard bath solution. First, we recorded electrically elicited compound action potentials (CAPs), at two sites along the PF path, to distinguish between activation and propagation failures. Increasing the bath temperature from 30

to 37 oC reduced the amplitude of the CAPs proportionally at the two recording electrodes. Further increase to 39 - 43 oC decreased the amplitudes of the CAPs at the distal electrode more than at the proximal one. This suggests that some APs failed to propagate between the two recording sites, due to the high temperature. Interestingly, when we used 4 stimuli with 10 or 20 ms intervals, the amplitude of the 4th CAP at the distal electrode was reduced less than the amplitude of the 1st CAP at 39 - 43 oC. We hypothesized that the depolarizing after-potential (DAP) following individual APs in PFs could facilitate the propagation of the APs that followed the first AP in the train. A 13-17% reduction of latency of 2nd, 3rd and 4th CAP, compared to the 1st one, supported our hypothesis. Furthermore, the similar drop in latency of CAPs 2-4 suggested that the level of depolarization provided by the DAPs were similar for all APs in the train. To support that suggestion we studied the shape of the DAP at temperatures between 30 and 41 oC using a grease-gap technique. We confirmed that the DAP was present in PFs in that temperature range. and the shape of the DAP was relatively similar after each CAP in 4-stimuli trains. As we have shown earlier, the DAP can also be recorded from the granule cell soma when antidromically travelling APs invade the soma. This somatic invasion can be prevented by hyperpolarizing the soma. We utilized a level of hyperpolarization that made approximately half of the APs fail to invade the soma. When the 1st AP propagated all the way to the soma, the following APs never failed. Our results suggest that the DAP can reduce conduction failures, in an activity dependent manner, in situations with reduced safety factor, e.g. during fever.

Disclosures: **D. Pekala:** None. **H. Szkudlarek:** None. **M. Raastad:** None.

Poster

577. Modulation of Neuronal Firing Properties I

Location: Hall A

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Support: Fondecyt Grant 1141170

Anillo Grant ACT1109

Fondecyt Grant 11100433

Conicyt Scholarship (RM) 2112079

Title: Size and dendritic localization of the axon initial segment correlates with *in vivo* spontaneous firing of individual substantia nigra dopaminergic neurons

Authors: *P. HENNY, R. C. MEZA;
Pontificia Univ. Catolica de Chile, Santiago, Chile

Abstract: In substantia nigra compacta (SNc) dopaminergic neurons the axon usually emerges from a primary or higher order dendrite. Actions potentials are generated at the most proximal region of the axon, the axon initial segment (AIS). This unmyelinated region is enriched in sodium and other ionic channels, as well as scaffolding proteins such as Ankyrin-G (Ank-G). As shown in other central neurons, the molecular composition, size and location of the AIS is known to influence the neuron's activity. In order to describe the mechanisms that influence firing in SNc dopaminergic neurons, we carried out a project to examine whether the structural characteristics of the AIS relate to the spontaneous tonic firing pattern showed by these neurons *in vivo*. Adult male mice SNc neurons were recorded under urethane anaesthesia. Neurons were recorded during spontaneous activity at least 15 minutes before neurobiotin labelling using the juxtacellular method, after which animals were perfused and their brains removed and serially sectioned. Neurons were revealed using streptavidin-Cy3 and identified as dopaminergic using immunofluorescence for tyrosine hydroxylase. To determine the shape and localisation of the AIS, entire individual neurons were traced and 3D reconstructed from labeled fragments acquired with a confocal microscope. The localisation of the AIS was confirmed using further immunofluorescence staining for Ank-G. Structural analysis show variable dendritic origin and size of the AIS in SNc dopaminergic neurons. The two variables nonetheless relate in that length of AIS diminishes with distance from the soma. Notably, electrophysiological analyses show that AIS length/localisation predicts spontaneous basal firing rate, in that neurons with large/proximal AIS fire faster than neurons with small/distal AIS.

Disclosures: P. Henny: None. **R.C. Meza:** None.

Poster

577. Modulation of Neuronal Firing Properties I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 577.12/C13

Topic: B.10. Intrinsic Membrane Properties

Support: NSF GRFP 2013165292

Title: Metabolic constraints on neuronal signaling

Authors: *M. L. GERTZ, Z. GREGURIC FERENCEK, Z. OBAIDA, J. R. CRESSMAN, Jr.;
George Mason Univ., Fairfax, VA

Abstract: Neuronal systems process information through action potential generation and transmission, synaptic transduction, and dendritic summation. These processes are driven by the dissipation of energy stored in the cells electrochemical gradients. Reduced gradients can significantly alter cellular function and ultimately lead to the failure of neuronal signaling. In order to maintain normal signaling, these gradients are reestablished through the conversion of ATP to ADP by the Sodium/Potassium pump. The concentration of ATP is primarily maintained through glucose metabolism. In order to elucidate the constraints on neuronal activity we use a conductance based model incorporating ionic dynamics and a simplified model of glucose metabolism. Ionic dynamics are modeled in thirteen compartments: three neuronal compartments, three glial compartments, six extracellular compartments and a vascular compartment. We utilize extracellular measurements of the potassium and oxygen responses from stimulation experiments performed in CA1 region of rat hippocampus to find the best fit values for parameters in our model. Here we utilize our calibrated model to investigate the limits of sustained and transient neuronal computation.

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Poster

577. Modulation of Neuronal Firing Properties I

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Program#/Poster#: 577.13/C14

Topic: B.10. Intrinsic Membrane Properties

Support: NIH Grant: RO1 NS044163

VA-BLR&D Merit Review: 821-MRNB-24218

Title: The roles of Kv2 channels in regular and burst firing of action potentials in layer 5a and 5b neocortical pyramidal neurons

Authors: *G. S. NEWKIRK[1], D. PATHAK[2], N. C. DEMBROW[1,3], R. C. FOEHRING[2], W. J. SPAIN[1,3];
[1]Physiol. & Biophysics, Univ. of Washington, Seattle, WA; [2]Dept. of Anat. & Neurobio., Univ. of Tennessee, Memphis, TN; [3]VA Epilepsy Ctr. of Excellence, Seattle, WA

Abstract: We used somatic current injection in layer 5 Pyramidal neurons in brain slices from 3-8 week old mice expressing either Etv1-EGFP, Glt25d2-EGFP or Thy1-h-YFP to study the role

of Kv2 type potassium channels on repetitive firing. Recordings were from somatosensory (layer 5a Etv neurons or layer 5b Glt neurons) or motor cortex (layer 5b Thy1 neurons) perfused with bicarbonate buffered Ringers, ACSF, at 33-35oC. Under control conditions, Etv1 neurons showed spike frequency adaptation whereas Glt neurons showed little change in firing rate following an initial doublet during constant depolarizing current injection via the whole-cell patch-pipette. In most Thy1 neurons, the onset of repetitive firing in response to the depolarizing current step was delayed. Firing then gradually increased in rate (warm-up firing) for the duration of the step. Burst firing was rare for any layer 5a or 5b neurons in ACSF. In order to block Kv2 containing channels, we added 100 nM Guangxitoxin (GxTX) to the ACSF. Changes in evoked firing to current steps in Etv1 neurons were similar to what was previously reported in rat pyramidal neurons: inter-spike trajectories became depolarized and the firing rate decreased for large stimuli but increased to small stimuli (i.e. the firing rate to current relation, F-I, became shallower). In most Glt neurons regular firing was converted to an initial burst and inter-spike trajectories were depolarized for the duration of the current step with an increase in firing rate (steeper F-I relation without a change in rheobase). In response to GxTX, most of the Thy1 cells displayed a repetitive bursting pattern; spikes were followed by an enhanced fast ADP and the bursts rode on a summated ADP envelope. In some neurons repetitive bursting persisted for the duration of the current step. Thy1 neurons that showed a repetitive bursting pattern to current steps also showed enhanced gain to the theta frequency components of a noisy current step (exponential filtered noise, tau = 5 ms with SD adjusted to cause a 2 mV SD of membrane voltage at rest was combined with DC current adjusted to give 5 or 20 Hz mean firing rate). Multiple lines of evidence implicate bursting emanating from layer 5b pyramidal neurons as an initiator of epileptic seizures. Recently, a human epilepsy was found to result from a mutation of the Kv8.2 subunit (Kv8 channelepsy). The seizure activity is thought to arise from altered activity of heteromeric Kv2.1/ mutant Kv8.2 channels. We hypothesize that Kv8 channelepsy is due to the conversion of layer 5b pyramidal neurons to a burst mode of firing by decreased Kv2 channel activity.

Disclosures: **G.S. Newkirk:** None. **D. Pathak:** None. **N.C. Dembrow:** None. **R.C. Foehring:** None. **W.J. Spain:** None.

Poster

577. Modulation of Neuronal Firing Properties I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 577.14/C15

Topic: B.10. Intrinsic Membrane Properties

Support: This work was supported by the National Institute for Neurological Disorders (RO1NS065761 to JMN and F32NS090765 to JLR)

Title: Genetic deletion of the sodium channel beta four subunit attenuates the Purkinje neuron resurgent sodium current and evoked firing frequency

Authors: *J. L. RANSDELL, P. M. ALLEN, J. M. NERBONNE;
Washington Univ., Saint Louis, MO

Abstract: The Sodium channel beta four subunit (Navβ4) is thought to play a pivotal role in the generation of the "resurgent" sodium current (I_{NaR}) and the ability of neurons to fire action potentials at high frequencies. Here, we generated a Navβ4 "knockout" mouse model (*Scn4b*$^{-/-}$) to investigate (1) the physiological role of Navβ4 in the regulation of sodium currents in Purkinje neurons (PNs) and (2) how these effects impact spontaneous and evoked PN firing. Previous studies have identified I_{NaR} in PNs and shown that this current generates an interspike depolarization and provides a mechanism for high frequency firing. I_{NaR} is thought to result from open-channel block of voltage-gated sodium channels by Navβ4 in competition with traditional sodium channel inactivation. This blocking Navβ4 particle is removed on repolarization, allowing resurgent sodium influx. Previous work has demonstrated that small interfering RNAs targeting Navβ4 diminishes I_{NaR} in cultured granule neurons and, although CA1 hippocampal neurons do not typically express I_{NaR}, intracellular addition of β4-like peptides produces I_{NaR}. These studies, while important in linking Navβ4 to the generation of I_{NaR}, do not directly demonstrate a physiological role for I_{NaR} in the generation of high frequency action potential firing. Here, we investigate the effects of *Scn4b* deletion on PN sodium currents and spontaneous and evoked firing in mature PNs. Current clamp recordings revealed no change in the spontaneous firing properties or in the waveforms of action potentials in *Scn4b*$^{-/-}$, compared with wild type (WT), PNs. However, the instantaneous firing frequency in response to depolarizing current injections is significantly ($p < .05$) attenuated in *Scn4b*$^{-/-}$ PNs. While we were unable to successfully clamp I_{NaR} in mature PNs, we find that the resurgent current in dissociated *Scn4b*$^{-/-}$ PNs is significantly attenuated (at -45mV *Scn4b*$^{-/-}$ = -306 ± 33pA, WT = -661 ± 43 pA, $p < .05$). These results indicate that loss of Navβ4 results in reduction of the I_{NaR} in PNs and impacts the ability of mature PNs to fire at high frequencies. Ongoing experiments are determining the effects of the loss of Navβ4 on the properties of the transient and persistent components of PN sodium currents. Further, to eliminate confounding influences of developmental and/or compensatory effects, we will determine the physiological effects of the acute knockdown of Navβ4 in adult PNs.

Disclosures: J.L. Ransdell: None. **P.M. Allen:** None. **J.M. Nerbonne:** None.

Poster

577. Modulation of Neuronal Firing Properties I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 577.15/C16

Topic: B.10. Intrinsic Membrane Properties

Title: Chronic intermittent hypoxic preconditioning in juvenile rats increases the intrinsic excitability of RVLM presympathetic neurons in response to acute hypoxia

Authors: M. KARLEN-AMARANTE[1], *D. ACCORSI-MENDONCA[2], C. E. L. ALMADO[1], D. J. A. MORAES[1], B. H. MACHADO[1];
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Abstract: The effects of acute hypoxia (AH) on the intrinsic electrophysiological properties of RVLM presympathetic neurons from rats exposed to chronic intermittent hypoxia (CIH) or normoxic condition were evaluated. Bilateral microinjections of a fluorescent retrograde tracer (rodamine retrobeads) into the intermediolateral column of spinal cord (T3-T5) were performed in anesthetized male *Wistar* rats (P 21) to label the bulbospinal RVLM presympathetic neurons. Two days later, rats entered the protocol of CIH or normoxic condition for 10 days. On the 11th day, rats were deeply anesthetized to obtain brainstem slices and only the labeled RVLM presympathetic neurons were recorded using *whole-cell patch-clamp*. The intrinsic electrophysiological properties were analyzed before and after AH, which was produced by slice superfusion with hypoxic solution (95% N_2 and 5% CO_2) during 2 min in the presence of fast synaptic blockers. Under this condition, all recorded RVLM presympathetic neurons presented intrinsic pacemaker activity. The baseline intrinsic firing frequency of recorded neurons from normoxic and CIH group were similar (normoxic = 5.77 ± 0.79 vs CIH = 6.27 ± 0.86). In the normoxic group, AH produced a significant decrease in the RVLM presympathetic neurons firing frequency (basal = 5.77 ± 0.79 vs AH = 4.94 ± 0.44; $p< 0.05$, n=32), but in CIH group AH produced a significant increase in relation to the baseline condition (basal = 6.27 ± 0.86 vs AH = 8.56 ± 1.12; $p< 0.05$, n=20). These data show that the AH decreased the firing frequency of RVLM presympathetic neurons in normoxic group, while CIH preconditioning induced an increase in their firing frequency in response to AH. ***Financial support:*** *FAPESP, CNPQ and CAPES.*

Disclosures: M. Karlen-Amarante: None. **D. Accorsi-Mendonca:** None. **C.E.L. Almado:** None. **D.J.A. Moraes:** None. **B.H. Machado:** None.

Poster

577. Modulation of Neuronal Firing Properties I

Location: Hall A

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Program#/Poster#: 577.16/C17

Topic: B.10. Intrinsic Membrane Properties

Support: CONICYT scholarship 21110650 (DK)

FONDECYT Grant 1140700

FONDECYT Grant 1140697

Title: Adaptation of the excitability of CA1 neurons to chronic inactivity

Authors: *D. KARMELIC, V. PALMA, M. SANHUEZA;
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Abstract: Correlation-based synaptic plasticity processes, such as long-term potentiation, generate positive feedback loops which by themselves result destabilizing for neuronal networks. This is prevented by a set of slower plasticity phenomena, termed 'homeostatic plasticity', acting in opposition to the changes in neural activity. These mechanisms include global scaling of the synaptic inputs to the neuron and changes in its intrinsic excitability through modification of different membrane conductances. Synaptic homeostatic plasticity of CA1 pyramidal neurons from organotypic hipocampal has been described in response to chronic inactivity, but it may not account for the robustness in the long-term firing rate observed *in vivo*. We therefore decided to study the homeostatic adaptation of the intrinsic excitability of CA1 principal cells in cultured slices. Using whole-cell recording we assessed, as a first step to describe such plasticity, the spiking frequency in response to depolarizing current injection in CA1 neurons from slices incubated in 1 μM TTX for 3 days compared to neurons from control slices. Neurons from TTX-treated slices show significantly more excitability, with higher firing frequencies at lower stimulation levels. We then measured the firing threshold using a current ramp and found no significant differences in this parameter, suggesting that changes in voltage-gated sodium channels do not explain the observed excitability increase. Resting membrane potential was also unchanged by the TTX treatment. Membrane resistance, on the other hand, increased considerably with chronic inactivity, from 105 ± 14 MΩ in control slices to 170 ± 31 MΩ in TTX-treated ones. Interestingly, blocking AMPA and $GABA_A$ receptors during the recording using CNQX and PTX, respectively, abolished almost completely the excitability differences, suggesting that the excitability increase in TTX-treated neurons is mainly the result of a decrease in the weight of synaptic conductances spontaneously open in CA1 neurons.

Disclosures: D. Karmelic: None. **V. Palma:** None. **M. Sanhueza:** None.

Poster

577. Modulation of Neuronal Firing Properties I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 577.17/C18

Topic: B.10. Intrinsic Membrane Properties

Support: KID funding

Title: Postnatal role of sox6 on maturation and function of cortical parvalbumin-expressing interneurons

Authors: *H. MUNGUBA[1], J. N. CARRIÇO[2], S. NILSSON[1], P. OBERST[1], A. B. MUNOZ-MANCHADO[1], R. BATISTA-BRITO[3], G. J. FISHELL[4], G. DI CRISTO[2], J. HJERLING-LEFFLER[1];
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Abstract: Cortical interneurons undergo extensive synaptogenesis and maturation of intrinsic properties during the first weeks after birth. In particular, parvalbumin (PV)-expressing basket cell interneurons go through a transcriptional profile shift during the second postnatal week, believed to be indispensable for their maturation. We have previously shown that basket cells lacking early expression of transcription factor Sox6 fail to properly migrate and mature electrophysiologically. Because Sox6 is still expressed in these cells throughout adolescent maturation, we are interested in investigating its role on late maturation and synaptic function and maintenance. We utilized a conditional knockout strategy to specifically remove Sox6 in interneurons at different postnatal stages. Our preliminary results suggest that Sox6 is important for basket cell interneuron maturation but not maintenance. To investigate synaptic maturation and function, we are exploiting a gene gun transfection approach allowing a detailed characterization of PV interneurons' axonal branching and bouton density onto excitatory neurons. Moreover, we are performing pair recordings of PV interneurons and pyramidal neurons in order to characterize the synaptic phenotype.

Disclosures: H. Munguba: None. **J.N. Carriço:** None. **S. Nilsson:** None. **P. Oberst:** None. **A.B. Munoz-Manchado:** None. **R. Batista-Brito:** None. **G.J. Fishell:** None. **G. di Cristo:** None. **J. Hjerling-Leffler:** None.

Poster

578. Glia, *In vivo* Approaches

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 578.01/C19

Topic: B.11. Glial Mechanisms

Support: CIHR Grant

AIHS fellowship

Title: Alteration to cerebral hemodynamics modifies astrocytes Ca^{2+} activity in awake, behaving mice

Authors: *C.-H. T. TRAN, G. GORDON;
Physiol. and Pharmacol., Univ. of Calgary, Calgary, AB, Canada

Abstract: The brain posses control mechanisms to regulate blood flow in order to meet metabolic demands. Functional hyperemia is an essential process in which increases in neural activity enhances cerebral blood flow. Astrocytes, which form an associated network with both neurons and blood vessels, have been shown to play a significant role in controlling blood flow accompanying changes in neural activity. Recent *in vivo* evidence conducted in anesthetized or slightly sedated animals questions the direct role of astrocyte intracellular Ca2+ in mediating functional hyperemia as spatial and temporal profile of astrocyte Ca^{2+} transients are poorly associated with the onset of vascular responses. Because anesthetics have dramatic effects on neural activity, astrocyte Ca2+ and hemodynamics, our objective was to uncover the spatiotemporal basis of the communication between astrocytes and the vasculature in fully awake, behaving mice. A craniotomy over the barrel cortex with the dura removed was performed. A custom build two-photon microscopy was used to image the vasculature and astrocytes Ca2+ from either C57Bl/6 mice or GLAST-cre-LSL-GCaMP3 mice or TEK-cre-LSL-ArchT3 mice. We found that 5-second whiskers' stimulation induced fast vasodilatory responses in penetrating arterioles but with endfoot and cell-wide Ca2+ transients that occurred with a delayed onset. Interestingly, the timing of these Ca2+ transients was typically observed at the peak of the sensory induced vasodilation. Thus, we tested the hypothesis that the vasculature communicates back to the astrocytes to modulate astrocytes Ca2+. We show that intraluminal perfusion of acetylcholine or phenylephrine alters cerebral hemodynamic responses that were followed by an alteration in astrocytes Ca2+ activity. To further test our hypothesis, we used a vascular endothelial specific promoter (TEK) to express archaerhodopsins (light-gated proton pumps that extrude protons from the cytoplasm to elicit hyperpolarization) to elicit vasodilation directly without neural or luminal manipulations. Activation of endothelial archaerhodopsins with brief application of yellow laser light induced fast vasodilation followed by an initiation of

endfoot Ca2+ transient. Our data redefine the uni-directional communication between astrocytes and the vasculature. We introduce a potential role of the vasculature as the modulator of astrocytes Ca2+ transients and propose that astrocytes may act as responders to changes in blood flow rather than rapid initiators of blood flow control.

Disclosures: **C.T. Tran:** None. **G. Gordon:** None.

Poster

578. Glia, *In vivo* Approaches

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 578.02/C20

Topic: B.11. Glial Mechanisms

Support: KAKENHI 22500285

KAKENHI 24111509

KAKENHI 26282217

KAKENHI 25116504

KAKENHI 24111509

KAKENHI 21500379

KAKENHI 25111703

Title: Glial involvement in transcranial direct current stimulation (tDCS)-induced plasticity

Authors: *H. MONAI[1], M. OHKURA[2], M. TANAKA[1], K. MIKOSHIBA[1], S. ITOHARA[1], J. NAKAI[2], Y. IWAI[1], H. HIRASE[1,2];
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Abstract: Transcranical direct current stimulation (tDCS) is a treatment known to ameliorate various neurological conditions and enhance memory and cognition in humans. tDCS has gained traction for its potential therapeutic value, however, little is known about its mechanism of action. Using a transgenic mouse expressing G-CaMP7 in astrocytes and a subpopulation of excitatory neurons, we find that tDCS induces large-amplitude astrocytic Ca2+ surges across the entire cortex with no obvious change in the local field potential. Moreover, visual evoked potential (VEP) in the visual cortex was enhanced after tDCS. The enhancement of VEP was

dependent on alpha-1 adrenergic receptor and was not observed in IP3R2 knockout mice in which astrocytic Ca2+ surges are absent. Notably, microglial ramification was visibly reduced by tDCS. Together, we propose that astrocytic Ca2+/IP3 signaling plays a significant role in tDCS-evoked neural changes with the electrical field as an adjuvant of neuron-glia interactions and plasticity.

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Poster

578. Glia, *In vivo* Approaches

Location: Hall A

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Topic: B.11. Glial Mechanisms

Support: FCT - PTDC/SAU-NSC/118194/2010

FCT - SFRH/BPD/97281/2013

FCT - SFRH/BD/89714/2012

EC - FP7-PEOPLE-2010-IEF 273936

BIAL Foundation Grant 61/2010

Title: The influence of astrocytic vesicular release on cognitive function

Authors: *J. F. OLIVEIRA[1], V. M. SARDINHA[2], S. GUERRA-GOMES[2], G. TAVARES[2], J. CORREIA[2], M. MARTINS[2], N. SOUSA[2];
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Abstract: Astrocytes are emerging as important actors in the regulation of synaptic transmission and plasticity. They possess unique morphologic and phenotypic features that allow them to monitor their neighbourhood and dynamically respond to changes. Since impairments of astrocytic function seem to have implications in neurotransmission, metabolism and brain homeostasis, we hypothesized that they will influence neural networks, ultimately underlying behaviour alterations. Astrocytes were described to release gliotransmitters (such as glutamate, GABA, ATP or D-Serine) by several mechanisms, namely through SNARE complex-dependent

vesicular release. This process, named gliotransmission, allows them to communicate with, and modulate vicinal cells, namely at the level of synapses. Yet, the consequences of gliotransmitter release to the network function remain to be elucidated. We used the dnSNARE model of gliotransmission impairment to assess behaviour alterations, namely on the cognitive domain. These results were paired with electrophysiological characterization of the neuro-glial networks in cortico-limbic regions intimately related with cognitive processing: prefrontal cortex and hippocampus. The combination of these techniques will surely provide us with crucial information on the role of astrocytes in the modulation of neural activity, impacting ultimately in cognitive processes.

Disclosures: **J.F. Oliveira:** None. **V.M. Sardinha:** None. **S. Guerra-Gomes:** None. **G. Tavares:** None. **J. Correia:** None. **M. Martins:** None. **N. Sousa:** None.

Poster

578. Glia, *In vivo* Approaches

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 578.04/C22

Topic: B.11. Glial Mechanisms

Title: Role of P2X7 receptor/HIF-1α signal pathway in astrocyte-mediated ischemic tolerance

Authors: *Y. HIRAYAMA[1,2], Y. IKEDA-MATSUO[3], S. KOIZUMI[2];
[1]Dept. Liaison Academy, Sch. Med., Univ. Yamanashi, Yamanashi, Japan; [2]Dept. Neuropharmacol., Interdisciplinary Grad. Sch. Med., Univ. Yamanashi, Yamanashi, Japan; [3]Dept. Pharmacol., Sch. Pharm. Sci., Univ. Kitasato, Tokyo, Japan

Abstract: In clinical settings, it is commonly observed that a mild ischemic episode protects neurons against a subsequent severe ischemic injury. This event is known as “ischemic tolerance”. Such short and mild ischemia, known as preconditioning (PC), itself does not cause brain damages, but instead, induces ischemic tolerance providing for future stronger injuries. We previously showed that PC-induced activation of astrocytes and subsequent upregulation of P2X7 receptor in these cells are essential for ischemic tolerance. However, a downstream signal(s) after activation of P2X7 receptor in astrocytes remains unknown. Here, we show that hypoxia inducible factor-1α (HIF-1α), a master molecule that induces various neuroprotective factors in neurons after ischemia, is responsible for the P2X7 receptor-dependent astrocyte-mediated ischemic tolerance in middle cerebral artery occlusion (MCAO) model *in vivo*. We investigated (1) spatiotemporal pattern of HIF-1α, (2) mechanisms underlying its upregulation, and (3) its pathophysiological consequence, showing difference in its roles between neurons and

astrocytes. (1) Using *in vivo* MCAO model in mice, we found that HIF-1α was expressed in both neurons and astrocytes after PC, but its spatiotemporal expression pattern in neurons was completely different from that in astrocytes. The upregulation of HIF-1α in neurons was early-onset and transient, whereas that in astrocytes was slow-onset and long-lasting (from 3 days ~). (2) Mechanisms underlying its upregulation were also different between neurons and astrocytes. The neuronal HIF-1α upregulation was dependent on oxygen (decrease), but astrocytic one was independent of oxygen but rather dependent on P2X7 receptor. We also confirmed these mechanisms using primary cultures of neurons or astrocytes. (3) Finally, we found that PC-induced upregulation in HIF-1α was essential for induction of ischemic tolerance. In P2X7 receptor-deficient mice, neither PC-induced ischemic tolerance nor HIF-1α upregulation in astrocytes was observed. On the contrary, PC could cause a transient HIF-1α increase in neurons but could not induce ischemic tolerance in these mice. Taken together, unlike a well-known oxygen-dependent pathway in neurons, astrocytes use a P2X7 receptor-mediated pathway to upregulate HIF-1α, thereby leading to induction of very strong ischemic tolerance.

Disclosures: **Y. Hirayama:** None. **Y. Ikeda-Matsuo:** None. **S. Koizumi:** None.

Poster

578. Glia, *In vivo* Approaches

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 578.05/C23

Topic: B.11. Glial Mechanisms

Support: the Ministry of Education, Culture, Sports, Science, and Technology (Japan)

Title: 7.0 Tesla MRI reveals electrostatic environment of the glia limitans

Authors: K. SUZUKI[1], K. YAMADA[1], Y. SUZUKI[1], I. L. KWEE[1,2], *T. NAKADA[1,2];
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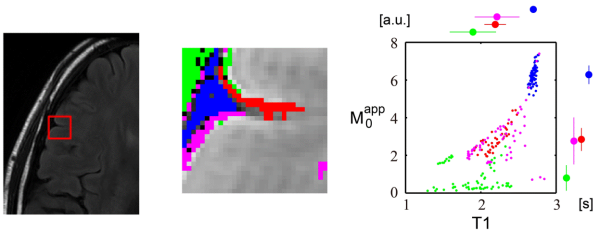
Abstract: Recently, fluid-attenuated inversion recovery (FLAIR) MRI on a 7.0T system revealed a high intensity “rim” at the cortical surface corresponding to the glia rich surface layer, often referred to as the glia limitans (TGL). TGL is identified by electron microscopy (EM) as an electron rich layer just beneath the pia matter that is primarily made of astrocyte end feet. In this study, we examined the intrinsic MRI parameters of TGL in normal human adults to determine its specific structural characteristics. The results revealed a rather unique combination of MRI parameters. Spin density was found to be ca. 50% of that of cerebrospinal fluid (CSF). T1 was ca. 20% shorter than that of CSF, whereas T2 was virtually identical to that of CSF. The

observed spin density and T2 characteristics indicated that GL contains free water molecules similar to CSF but at almost half in density. The significantly shorter T1 of long T2 free water molecules implies that there is a nearby structure which facilitates T1 relaxation similar to ionic contrast agents. TGL is rich in the water channel aquaporin-4 (AQP-4), and as demonstrated by EM, TGL comprises a structure which can accumulate electrons under appropriate conditions. Given these anatomical characteristics, the unique MRI properties of TGL can only be explained as follows. TGL has a relatively low density of free water due to the functionality of AQP-4. This relatively "dry" condition establishes an electrostatic environment. Brain activities continuously provide electrons to flow through the cortex which can be trapped in TGL due to its electrostatic environment. The low free water density accounts for the low spin density with long T2. Facilitated energy exchange between spin and electrons results in a paradoxically short T1 for these free water molecules. The study represents the first direct support of the vortex theory of the brain (Nakada T, Cytotechnol 2009;59:145) which predicts that human association cortex is a biological realization of Kohonen's self-organizing map (Kohonen T, Proceeding of the IEEE 1990;78:1464).



Disclosures: **K. Suzuki:** None. **K. Yamada:** None. **Y. Suzuki:** None. **I.L. Kwee:** None. **T. Nakada:** None.

Poster

578. Glia, *In vivo* Approaches

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 578.06/C24

Topic: B.11. Glial Mechanisms

Title: Increased expression of astrocytic connexins in AQP4 knockout mice

Authors: *S. KATOOZI, L. M. A. CAMASSA, S. RAHMANI, H. B. BOLDT, O. P. OTTERSEN, M. AMIRY-MOGHADDAM;
Univ. of Oslo/ Inst. of Basic Med. Sci., Oslo, Norway

Abstract: Aquaporin-4 (AQP4) is the predominant water channel in the brain. It is expressed in high density at the astrocyte endfeet membrane domains surrounding brain microvessels. AQP4 is colocalized with the inwardly rectifying potassium channel Kir4.1, leading to the suggestion that AQP4 is involved in K^+ homeostasis. However, AQP4-knockout (AQP4-KO) mice show a rather mild phenotype without any impairment of K^+ clearance. A recent study has shown facilitated K^+ redistribution and enhanced tracer coupling among astrocytes in the hippocampus of AQP4-KO mice (Strohschein et al. 2011). Based on this, we hypothesized that a compensatory increase in the expression levels of astrocytic connexins could explain the mild phenotype of AQP4-KO mice in regard to K^+ homeostasis. We investigated the expression and distribution of the two astrocytic connexins Cx43 and Cx30 in the brains of wild type (WT) and AQP4-KO mice. Using Western blotting we show that the expression levels of both Cx43 and Cx 30 are increased in AQP4-KO brains compared with WT. Moreover, immunogold analysis of parietal cortex and hippocampus show that the number of gap junctions per capillary profile and the number of connexins per gap junction are increased in the AQP4-KO mice. The most pronounced changes were observed in hippocampus where the number of connexin labelled gap junctions per capillary profile increased by 100% following AQP4 knockout. Our results provide a mechanistic basis for the facilitated K^+ redistribution, enhanced tracer coupling, and mild phenotype characteristic of AQP4-KO mice. *The first two authors contributed equally to this work.

Disclosures: S. Katoozi: None. **L.M.A. Camassa:** None. **S. Rahmani:** None. **H.B. Boldt:** None. **O.P. Ottersen:** None. **M. Amiry-Moghaddam:** None.

Poster

578. Glia, *In vivo* Approaches

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 578.07/C25

Topic: B.11. Glial Mechanisms

Support: MDA

Title: 3D modeling, tissue reconstruction, and quantification of astrocyte distribution in the adult mouse CNS at molecular resolution with intact thick tissue matter

Authors: *R. G. SATTLER, S. J. MILLER, J. D. ROTHSTEIN;
Brain Sci. Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: Astrocytes are the most abundant cell type in the central nervous system (CNS). To date, astrocyte studies have focused on isolated anatomical locations of interest but fail to appreciate distribution across the whole CNS. Large regional quantification of astrocyte distribution and molecular subtypes of astrocytes may enable a better understanding of glial contributions to CNS disease. Furthermore, these imaging and molecular labeling tools may provide insight into affected areas previously undetected. In order to evaluate astrocyte distribution across the entire CNS, we performed the recently established method, CLARITY. Using a double transgenic mouse line that has unique, astroglial specific genetically encoded fluorescence reporters to visualize all protoplasmic astrocytes and an astrocyte subpopulation, we quantified the overall distribution throughout the CNS. This method also allows one to stain and re-stain tissue without destroying cellular structures or biological targets of interest. In addition, for the first time, we present a further optimized system that includes sequential sectioning of fixed tissue, 3D remodeling of cell structures, tissue reconstruction, and *in vivo* astrocyte specific quantification. Taken together, we believe this optimized method should be utilized to study astrocytes and other glia at molecular resolution across thick tissue matter in normal as well as diseased CNS.

Disclosures: R.G. Sattler: None. **S.J. Miller:** None. **J.D. Rothstein:** None.

Poster

578. Glia, *In vivo* Approaches

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Program#/Poster#: 578.08/C26

Topic: B.11. Glial Mechanisms

Support: Fapesp

CAPES

CNPq

Title: Establishing a novel two-photon imaging approach to access spinal motoneurons *in vivo*

Authors: *L. P. CARTAROZZI[1], A. SCHELLER[3], F. KIRCHHOFF[3], A. L. R. OLIVEIRA[2];
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Abstract: Following axotomy, spinal motoneurons undergo chromatolysis, which is a retrograde reaction that takes place in the cell body. Such process leads to retraction of dendrites, synaptic stripping and a shift from transmitting phenotype to regenerative state. Several molecules related to the regenerative response are upregulated, allowing regrowth of the axon. A hallmark of the response to lesion is the rapid activation of astrocytes and microglia nearby affected motoneuron cell bodies, disturbing the pre-synaptic inputs. With the advent of *in vivo* imaging, new studies regarding fine changes related to neuronal/glial reaction following acute lesion can potentially be carried out. Recent reports have used advanced light microscopy approaches, such as two-photon laser scanning microscopy (2P-LSM), in combination with fluorophores/fluorescent proteins to image the CNS aiming to access cellular responses of glial cells after peripheral nerve injury. Of particular interest, temporal activation and role of different glial cells that become activated after lesion needs further investigation. So far, imaging of the spinal cord has been largely restricted to the superficial white matter of the dorsal horn, mostly due to the easier surgical approach. In turn, evaluation of deeper regions of the spinal cord, especially the ventral horn is challenging. However, it may provide a better understanding of the early motoneuron response to injury, allowing direct visualization of fast Ca2+ neuronal changes or structural alterations related to neuron/glia interactions. The present work aimed at establishing a new methodology to image spinal motoneurons *in vivo*, employing two-photon microscopy. For that purpose, we used the following transgenic mice: TgN(GFAP-eCFP) and TgH(CX3CR1-EGFP). The retrograde tracer Fluororuby was unilaterally injected in the gastrocnemius muscle from double transgenic mice in order to label motoneurons from the sciatic nerve pool. Six days after tracer injection, lumbar vertebrae laminectomy allowed exposure of the lateral aspect of the spinal cord at the lumbar intumescence for *in vivo* imaging. The results demonstrate that using a combination of transgenic animal models, retrograde tracer injection, 2P-LSM and appropriate surgical techniques makes possible *in vivo* imaging of deep spinal cord laminae, allowing motoneuron and circumjacent glial cells to be localized and evaluated in a real time fashion.

Disclosures: L.P. Cartarozzi: None. **A. Scheller:** None. **F. Kirchhoff:** None. **A.L.R. Oliveira:** None.

Poster

578. Glia, *In vivo* Approaches

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 578.09/C27

Topic: B.11. Glial Mechanisms

Support: 2R01NS036692

5R01NS031234

1F3NS074597

1R01NS082851

Title: Vessel-associated glioma cells co-opt vascular regulation

Authors: ***I. KIMBROUGH**, A. HONASOGE, L. CHAUNSALI, H. SONTHEIMER; Neurobio., Univ. of Alabama At Birmingham, Birmingham, AL

Abstract: Functional hyperemia is important to normal brain functioning. Glioma cells on the vasculature interfere with normal physiology by breaking the astrocytic endfoot attachment to the basement membrane (BM) of blood vessels, leaving them unresponsive to astrocyte-released vasoactive signals. Glioma co-option of vascular regulation can occur directly, through release of vasoactive molecules onto smooth muscle cells, or indirectly, through activation of astrocytic receptors, and subsequent release of vasoactive molecules. Chronic vasodilatory regulation through release of prostaglandins or K+, may lead to a persistent shunting of blood flow to a growing tumor. Alternatively, acute regulation of vasoconstriction by invading glioma cells, through release of arachidonic acid or high K+, could cause a transient decrease in vessel tone, enlarging the perivascular space for invasion. Therefore, co-option of vascular regulation is important to glioma cell survival, as vessel dilation may assure improved nutrient delivery, and constriction may facilitate invasion along the vasculature. In this study, we investigate how invading glioma cells regulate vascular coupling. We generated D54GCaMP3/Mrga1 glioma cells (MrgA1) expressing both GCaMP3 and RASSL (receptor activated solely by synthetic ligand). GCaMP3 is a GFP-bound Ca2+ sensor, while the RASSL (Mrga1) is tied to the TdTomato red fluorescence protein. The RASSL receptor is an artificial g-protein coupled receptor (GPCR) not expressed in mammalian cells. It is activated by FMRF, an exogenous and specific ligand, and induces an increase in intracellular Ca2+. Using time-lapse volumetric confocal microscopy and 3D reconstructions we show that bath application of FMRF on cultured Mrga1 cells leads to transient Ca2+ rises followed by changes in cell morphology and increased invasion. In acute slice experiments we show Mrga1 activation leads to transient Ca2+ rises in arteriole associated glioma cells followed by changes in vessel diameter. This effect was diminished in the presence of the K+ channel inhibitors Tram-34 and Paxilline suggesting that K+ release contributes to glioma-mediated vascular regulation. Using *in vivo* video time-lapse multi-photon microscopy, we show that activation of arteriole associated Mrga1 cells also leads to transient Ca2+ rises followed by vessel diameter changes. These diameter changes also diminished with K+ channel inhibitors. Taken together, our data suggest that gliomas are capable of assuming control of the vasculature along which they are invading, through a process that is Ca2+ dependent, likely involving Ca2+ activated K+ channels.

Disclosures: I. Kimbrough: None. **A. Honasoge:** None. **L. Chaunsali:** None. **H. Sontheimer:** None.

Poster

578. Glia, *In vivo* Approaches

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 578.10/C28

Topic: B.11. Glial Mechanisms

Support: The study was financed by Aleva Neurotherapeutics (manufacturer of the DBS electrodes used in the experiments)

Title: The time course of the glial reactivity to deep brain stimulation. A longitudinal study of DBS in the Goettingen Minipig brain

Authors: *D. ORLOWSKI[1], A. MICHALIS[2], A. N. GLUD[1], A. R. KORSHØJ[1], L. M. FITTING[1], T. W. MIKKELSEN[1], A. MERCANZINI[2], A. JORDAN[2], A. DRANSARD[2], J. C. H. SØRENSEN[1];
[1]The Dept. of Neurosurg., Dept. of Clin. Medicine, Aarhus Univ., Aarhus C, Denmark; [2]Aleva Neurotherapeutics SA,, Lausanne, Switzerland

Abstract: The use of Deep Brain Stimulation (DBS) is constantly growing, and its indications include not only treatment of movement disorders, but also therapy of chronic pain, obesity, drug resistant psychiatric disorders and even Alzheimer disease. Despite broader use of DBS, the number of studies on analyzing the reaction of the brain tissue to the implanted electrode, especially in large animal models, is still very limited. In our experiment we tested DBS electrodes in a large animal model - the Goettingen minipigs. Twelve animals (females) were used in this study, one control and eleven with bilaterally implanted DBS electrodes into anterior striatum. 3, 6 and 12 months after implantation animals were sacrificed, perfused with 10% formalin and the brains were removed. Following 5 days of immersion in 30% sucrose the brains were divided into two hemispheres and tissue blocks containing electrode track were dissected free, embedded in OCT and frozen in isopentane cooled by dry ice. The brain tissue was sectioned into transversal 40µm sections containing electrode track using cryomicrotome and stained using Nissle and Eosine, anti-GFAPab or isolectin. The tissue reaction was analyzed on five levels following from the tip of the electrodes, in order to compare tissue response to the stimulation with non-stimulated tissue: four along the active part of the electrode (contacts areas), and the fifth lying approx. 5 mm above contacts (control areas). The sections were described both qualitatively and quantitatively. Quantitative assessment of the reaction to the implanted electrode was based on the semi-automatic measurement of the area covered by the staining. The areas of the tissue reaction and thickness of the glial scar were measured using the Fiji (ImageJ) program on microphotographs of the tissue areas of the sections containing

electrode track. Moreover, two independent blinded observers tried to differentiate histological response induced by stimulated versus non-stimulated electrodes on the basis of qualitative observations. Results and conclusions: Tissue reaction was limited to the relatively small area around the electrode and should be considered as a minor to mild reaction. The temporal pattern of the reaction indicates that tissue response stabilized over the time (reaction after 12 months were lower than after 6 months). We found no histological evidence that stimulated part of the electrode can trigger different tissue response than its non-stimulated part.

Disclosures: **D. Orlowski:** None. **A. Michalis:** A. Employment/Salary (full or part-time):; Aleva Neurotherapeutics SA, Lausanne, Switzerland. **A.N. Glud:** None. **A.R. Korshøj:** None. **L.M. Fitting:** None. **T.W. Mikkelsen:** None. **A. Mercanzini:** A. Employment/Salary (full or part-time):; Aleva Neurotherapeutics SA, Lausanne, Switzerland. **A. Jordan:** A. Employment/Salary (full or part-time):; Aleva Neurotherapeutics SA, Lausanne, Switzerland. **A. Dransard:** A. Employment/Salary (full or part-time):; Aleva Neurotherapeutics SA, Lausanne, Switzerland. **J.C.H. Sørensen:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Aleva Neurotherapeutics SA, Lausanne, Switzerland.

Poster

578. Glia, *In vivo* Approaches

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 578.11/C29

Topic: B.11. Glial Mechanisms

Support: MPFI

Title: Subcellular organization of the orientation map in visual cortical astrocytes

Authors: M. LÓPEZ-HIDALGO, *J. SCHUMMERS;
Max Planck Florida Inst., Jupiter, FL

Abstract: The analysis of calcium responses in astrocytes started a new era of understanding how these cells interact with neuronal circuits. Astrocytes respond with calcium elevations to sensory stimulation including visual stimulation. Previous work done in ferrets showed that astrocytes somas in visual cortex are tuned to visual stimuli with a similar spatial arrangement to neurons but with sharper orientation tuning curves. Advances in calcium imaging techniques as well as the use of genetically encoded calcium indicators now permit the analysis of visual-

evoked responses in the entire territory of astrocytes. Here, we studied the spatial and temporal dynamics of calcium responses in ferret visual cortex astrocytes expressing GCaMP6s (under control of the GFAP promoter) using two-photon laser scanning microscopy. We find robust visually-evoked calcium responses in processes throughout the entire territory of individual astrocytes. Our results show that the orientation tuning of these responses in astrocyte processes match the orientation map. In agreement with this, astrocytes located near pinwheel center have a gradual change in the tuning curve across their territory, representing a subcellular organization of the orientation map. More generally, this result suggests that astrocytes respond with extraordinary spatial specificity to local synaptic activity *in vivo*.

Disclosures: **M. López-Hidalgo:** None. **J. Schummers:** None.

Poster

578. Glia, *In vivo* Approaches

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 578.12/C30

Topic: B.11. Glial Mechanisms

Support: NIH Grant R01 MH099564

Title: Behavioral characterization of astrocyte Gs conditional knockout mice

Authors: *A. MADAYAG, K. M. BOYT, K. D. MCCARTHY;
Pharmacol., UNC Chapel Hill, Chapel Hill, NC

Abstract: Astrocytes are the most abundant cell type in the mammalian brain and exist in close proximity to other cells of the central nervous system, including neurons. Interestingly, astrocytes express many of the same receptors and signaling pathways as neurons. This lends the difficult task of dissecting the role of astrocyte signaling in brain function. Unfortunately, standard pharmacological methods lack cell specificity. Our laboratory utilizes astrocyte targeted transgenic and conditional knockout (cKO) models to investigate the role of astrocyte signaling in physiology, behavior, and pathology. Gs G-Protein Coupled Receptors (GsGPCR) are among the many signaling pathways expressed by both astrocytes and neurons and have been implicated in numerous neuro-pathological disorders. We generated a mouse line that affords us the ability to genetically recombine the Gs gene, and thus silence ligand-induced activation of GsGPCR signaling pathways in astrocytes. To inactivate GsGPCR signaling in astrocytes, adult GFAP:CreER^{T2}::Gs$^{flox/flox}$ (cKO) and Gs$^{flox/flox}$ (littermate control) mice were given 5 consecutive daily doses of tamoxifen (200mg/Kg, gavage) to activate inducible Cre-recombinase. We

previously reported that mice lacking astrocytic GsGPCR signaling (cKO) exhibited intact contextual memory in the Morris Water Maze and locomotion in an open field, and deficits in sensorimotor gating as measured by prepulse inhibition. Consistent with our previous findings, here we report that cKO mice exhibit intact contextual and cue memory as measured in a fear conditioning paradigm. We also measured normal social interaction as measured in a social preference paradigm. Conversely, we observed decreased open arm time by cKO mice in an elevated plus maze paradigm, suggesting an anxiogenic phenotype. Male, but not female cKO mice show hyperactivity to an amphetamine challenge, suggesting altered reward or corticostriatal neurocircuitry. Our findings suggest that Gs and thus GsGPCR signaling in astrocytes is important in certain animal behavior, however the lack of phenotypic differences in the majority of behavioral paradigms is surprising. It is important to verify the selectivity of the inducible Cre model. To do this, we have chosen to cross the GFAP:CreER^{T2} to multiple reporter lines of mice as this is more sensitive than measuring Cre expression with immunohistochemical staining. To further the field, we are interested in continuing our characterization of this genetic model in more complex behavioral tasks as well as isolate mechanisms that may contribute to observed phenotypes.

Disclosures: A. Madayag: None. **K.M. Boyt:** None. **K.D. McCarthy:** None.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.01/C31

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Grants-in-Aid for Japan Advanced Molecular Imaging Program and Science Research

Grant-in Aid for Scientific Research on Innovative Areas (Brain Protein Aging and Dementia Control) 26117008 from MEXT

Title: Longitudinal *in vivo* imaging of tau pathology, microglial activation and neuronal loss in a mouse model of tauopathy

Authors: *N. SAHARA, A. ISHIKAWA, M. TOKUNAGA, T. MINAMIHISAMATSU, J. MAEDA, M. SHIMOJO, M. ONO, S. UCHIDA, I. MATSUMOTO, H. TAKUWA, M.-R. ZHANG, T. SUHARA, M. HIGUCHI;
Natl. Inst. of Radiological Sci., Chiba, Japan

Abstract: Accumulation of intracellular neurofibrillary tangles consisting of microtubule-associated protein tau is a major hallmark of tauopathy. Recent advances in positron emission tomography (PET) imaging research have led to significant breakthroughs with newly developed probes for tau depositions. This technology allows us to noninvasively examine the tau pathogenesis in living brains of humans and animal models. Our previous study has demonstrated that PET imaging with a tau radioligand, [^{11}C]PBB3, clearly visualizes tau deposits, which is closely aligned with disease symptoms. Here, we conducted a longitudinal PET and magnetic resonance imaging (MRI) of transgenic mice modeling tauopathy (rTg4510) and non-transgenic controls from 2 to 13 months of age, in order to examine the utility of small-animal *in vivo* imaging for pursuing links between tau deposition and neurodegeneration. Along with [^{11}C]PBB3, microglial activation was also visualized using a radioligand for the 18-kDa translocator protein (TSPO), [^{11}C]Ac-5216. In the rTg4510 mice, tau accumulation, neuroinflammation and forebrain atrophy became noticeable at 6 months of age, and retentions of tau and TSPO radioligands were inversely correlated to neocortical volumes. Postmortem immunohictochemical assays revealed that elevated TSPO signals in putative microglia were associated with accumulation of tau inclusions in the neocortex and hippocampus of rTg4510 mice. Our results indicate that temporospatial relationship among tau deposition, neuroinflammation and neuronal loss can be pursued by *in vivo* imaging of animal models. Non-invasive PET imaging combined with transgenic mouse models can be a powerful experimental tool to investigate mechanisms of neurodegenerative disease and evaluation of therapeutic interventions.

Disclosures: **N. Sahara:** None. **A. Ishikawa:** None. **M. Tokunaga:** None. **T. Minamihisamatsu:** None. **J. Maeda:** None. **M. Shimojo:** None. **M. Ono:** None. **S. Uchida:** None. **I. Matsumoto:** None. **H. Takuwa:** None. **M. Zhang:** None. **T. Suhara:** None. **M. HIguchi:** None.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.02/C32

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Conacyt Grant 127357 (JS)

Title: A cellular model of tau-mediated NMDA receptor dysfunction

Authors: *E. E. PEREZ SOLIS, J. SEGOVIA-VILA, U. GARCÍA;
CINVESTAV, Gustavo A. Madero, Mexico

Abstract: Alzheimer's disease is characterized by the presence of two insoluble aggregates: amyloid plaques and neurofibrillary tangles. These aggregates participate in the neurodegenerative process underlying the cognitive deficits associated with this type of dementia. However, the main components of the aggregates, the amyloid peptide and tau protein, have neurotoxic effects prior to the formation of insoluble aggregates. It is considered that neuronal dysfunction begins at least 20 years before the appearance of clinical symptoms, when a synaptic deficit is already modifying the single and network properties of neurons, setting the stage for further deterioration of brain activity. Tau protein has come to be considered the effector of amyloid beta toxicity, because its multiple post-translational modifications change neuronal structure and signalling pathways. We are interested in the role that tau protein has in regulating the activity of receptors associated with learning, memory and toxicity, such as the NMDA-type glutamate receptor, a target of amyloid beta. Using the HEK293 and SH-SY5Y cell lines as models, we expressed both the eYFPNR-1A and eGFP-NR2B subunits, as well as the full sequence of tau protein, allowing us to have a functional receptor which activity is recorded through whole-cell patch clamp technique. In this condition we found that when tau protein is overexpressed the total evoked current of the NMDA receptor increases, suggesting this might be related to neurotoxicity. Tau protein undergoes a series of post-translational modifications such as phosphorylation and proteolysis that endow it with pathological characteristics. It has been previously reported that among these modifications proteolysis is a key one. A fragment of tau that comprises from amino acid 297 to 391 (three and half microtubule binding domain) has a greater capacity to form insoluble aggregates, it is present since the early stages of neurofibrillary tangle formation and increases in severe cases of Alzheimer's disease, however, it is not yet known whether it may affect synaptic function. We are currently testing if this fragment modifies the activity of the NMDA receptor in both cell lines, and the effect that tau aggregation has in the sensitivity to amyloid beta toxicity. This will give us a better understanding of how post-translational modifications and aggregation of tau affect the activity of the NMDA receptor and the role they play in Alzheimer's disease.

Disclosures: E.E. Perez Solis: None. **J. Segovia-Vila:** None. **U. García:** None.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.03/C33

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: CIHR

Brain Canada

Title: Numb regulates Tau levels and axonal homeostasis in mouse retinal ganglion cells

Authors: *M. LACOMME, ESQ[1], J. CAI[1], M. CAYOUETTE[1,2,3];
[1]Inst. De Recherche Clinique De Montréal, Montreal, QC, Canada; [2]Dept. of Medicine, Univ. de Montréal, Montreal, QC, Canada; [3]Anat. and Cell Biol. department, McGill Univ., Montreal, QC, Canada

Abstract: Disruption of axonal structure or function can have devastating consequences for neuronal survival, as observed in various neurodegenerative diseases, but the mechanisms involved in the maintenance of axonal homeostasis remain poorly understood. Various studies have shown that endocytosis and vesicular trafficking is critical for neurite growth and survival. One particularly interesting endocytic player is the adaptor protein Numb, but its function in postmitotic neurons remains unclear. We therefore hypothesized that Numb might regulate vesicular trafficking of proteins involved in the maintenance of axonal structural integrity and neuronal survival. To address this question, we generated a conditional knockout (cKO) mouse of Numb (and its homolog Numblike) in retinal ganglion cells (RGCs) using the Cre/lox system. Although total RGC number was not altered in cKO at 6 months, we observed axonal swelling in cKO RGCs both *in vitro* and *in vivo*, suggesting altered axonal integrity that might increase susceptibility to cellular stress. To test this idea, we injected NMDA in the eyes of cKO and control mice and studied RGC survival 3 days later. Interestingly, while about 50% of RGCs were lost in control retinas, we found that more than 80% of RGCs degenerated in cKO, indicating that Numb is required to prevent RGC degeneration, at least under these conditions. Molecularly, we found that the levels of the microtubule-associated protein Tau were sharply increased in Numb cKO optic nerves, likely explaining the axonal swelling observed in cKO and the increased neuronal susceptibility to injury. Consistent with this idea, we found that Tau overexpression in RGC phenocopies Numb inactivation and causes axonal swelling, whereas siRNA-mediated knock-down of Tau rescues RGC death observed in Numb cKO after NMDA injury. Finally, co-immunoprecipitation experiments indicate that Numb interacts with Tau, suggesting a model in which Numb might function as an adaptor protein to control the endocytic trafficking of Tau in RGC axons. Together, these results identify Numb as an essential player in the maintenance of axonal homeostasis, possibly by regulating the trafficking of Tau proteins. Interestingly, anatomical changes have been detected in eyes of Alzheimer's disease patients before signs of cognitive impairment and because alteration in Numb isoform levels were observed in Alzheimer's patients and transgenic mutant mice, our findings point to a possible molecular mechanism underlying increased neuronal susceptibility in neurodegenerative diseases involving accumulation of Tau proteins.

Disclosures: **M. Lacomme:** None. **J. Cai:** None. **M. Cayouette:** None.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant K01AG039386

Schott Foundation

UCSF SOM REAC award (Mainprice Memorial Foundation and Cox J. Fund)

Title: Brain aggregates; an effective *in vitro* cell culture system for drug screening targeting neurodegenerative diseases

Authors: *M. AHN[1], F. KALUME[2], A. OEHLER[1], R. PITSTICK[3], G. CARLSON[3], S. DEARMOND[1];
[1]Dept. of Pathology, UCSF, San Francisco, CA; [2]Dept. of Neurolog. Surgery and Pharmacol., Universtiy of Washington, Seattle, WA; [3]McLaughlin Res. Inst., Great Falls, MT

Abstract: Drug discovery for neurodegenerative diseases is very challenging because we often find discrepancies in drug efficacy from *in vitro* and *in vivo* studies. Current cell-culture systems used for *in vitro* drug screening assays suffer from many limitations. First, few cell-culture systems accurately model aging or neuropathological progression of neurodegenerative diseases in the brain. Second, drug efficacy can vary in different cell types such as dividing vs. stationary cells; the latter resembles non-dividing neurons in the brain. Drug screening for neurodegenerative diseases should be performed in non-proliferating neural cells. Brain aggregate culture (BrnAggs) derived from mouse brains at embryonic day 15 is a 3 dimensional sphere-shaped cell culture consisting of neurons, astrocytes, oligodendrocytes and microglia. We previously showed that they accurately represent neuropathogenic characteristics of prion disease (progressive accumulation of PrPSc and dendritic degeneration) and reflect *in vivo* efficacy of anti-prion compound effectively. Here, we optimized the BrnAgg preparation method suitable for a 96-well plate format drug screening assay and found that BrnAggs form functional networks by measuring field potential activities. Lastly, we examined whether BrnAggs can model tauopathies. We found similar neuropathological characteristics of tauopathies (increased phopshoprylated tau, ThioS-positive amyloids and dendritic degeneration) in aged BrnAggs

prepared from Tg 4510 mice expressing human tau with a P301L mutation. Infection with Tg 4510 mice brain homogenates exaggerates tau pathology in these BrnAggs. BrnAggs are 3D cell culture resembling neural components of the brain and can be prepared from many varieties of transgenic mouse models of neurological diseases such as epilepsy and tauopathies. We believe BrnAggs will serve as an effective *in vitro* cell culture system for drug discovery of many neurological diseases.

Disclosures: **M. Ahn:** None. **F. Kalume:** None. **A. Oehler:** None. **R. Pitstick:** None. **G. Carlson:** None. **S. DeArmond:** None.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.05/C35

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Owens Family Foundation

NIH

University of Virginia President’s Fund for Excellence

Fraternal Order of Eagles

Webb and Tate Wilson

Title: Extracellular tau oligomers induce mislocalization of endogenous neuronal tau and axonal transport deficits

Authors: ***E. M. SWANSON**, L. MCMAHON, L. BRECKENRIDGE, S. SOM, G. S. BLOOM; Univ. of Virginia, Charlottesville, VA

Abstract: Tau is a neuron-specific, microtubule-associated protein enriched in axons, where its functions include direct binding and stabilization of microtubules, and regulation of axonal transport. CNS tau comprises six isoforms produced by the alternative splicing of a single tau gene, MAPT, with these isoforms characterized by the presence of zero, one or two N-terminal inserts, and three or four C-terminal microtubule binding repeats. Neuronal inclusions composed of hyperphosphorylated tau are a major histopathological feature of a series of neurodegenerative disorders known collectively as tauopathies, of which Alzheimer’s disease (AD) is the most

prominent. While the clinical and histological presentation of these disorders is heterogeneous, the majority share the following hallmarks: loss of the normal axonal distribution of tau; accumulation of insoluble, fibrillar tau aggregates in neurites and perikarya; synaptic dysfunction; and eventual neuron death. Familial mutations identified in the MAPT gene point to a causative role for tau in these disorders, with changes in the isoform ratio or aggregation propensity of tau causing fully penetrant neurodegenerative diseases. In this study, we demonstrate that externally applied oligomeric tau cause a loss of normal tau distribution within primary cortical neurons. Utilizing a quantitative assay to measure the extent of tau aggregation in cultured neurons, we demonstrate that tau oligomers are much more effective than tau monomers or fibrils at inducing tau redistribution within axons, that the extent of this disruption varies according to tau isoform, and that oligomers made from mixtures of all six CNS tau isoforms are much more potent than oligomers made from individual isoforms. Tau is known to play an integral role in the regulation of cargo transport along axonal microtubules, and we also show that this tau aggregation causes alterations in the normal, microtubule based trafficking of various classes of axonal membrane-bounded organelles. Cells treated with oligomeric tau showed significant increases in the anterograde velocity and run lengths of dense-core vesicle transport marked by neuropeptide-Y or BDNF, and lysosome trafficking was similarly affected. These results raise the possibility that soluble, pre-fibrillar oligomers of varying tau isoforms account for the prion-like spread of tau pathology *in vivo* in AD and non-Alzheimer's tauopathies, and point to mechanisms by which loss of physiological tau distribution lead to neuronal dysfunction.

Disclosures: **E.M. Swanson:** None. **L. McMahon:** None. **L. Breckenridge:** None. **S. Som:** None. **G.S. Bloom:** None.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.06/C36

Topic: C.02. Alzheimer's Disease and Other Dementias

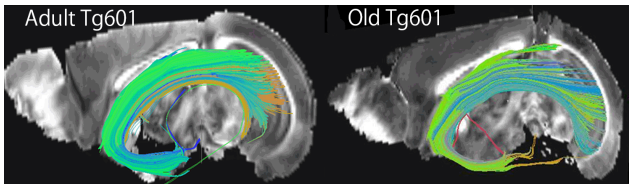
Support: Ministry of Education, Culture, Sports, Science, and Technology of Japan

Brain Mapping by Integrated Neurotechnologies for Disease Studies

Title: Selective involvement of the septo-hippocampal fiber tract and upregulation of acetylcholinesterase in tauopathy model mice

Authors: *Y. MOTOI[1], Y. HARA[1], K. HIKISHIMA[2], H. MIZUMA[3], H. ONOE[3], S.-E. MATSUMOTO[1], H. OKANO[2], S. AOKI[1], N. HATTORI[1];
[1]Juntendo Univ. Sch. Med., Tokyo, Japan; [2]Keio Univ. Sch. of Med., Tokyo, Japan; [3]RIKEN Ctr. for Life Sci. Technologies, Kobe, Japan

Abstract: Background: Cholinergic cell loss in the basal forebrain, the major source of hippocampal cholinergic projections, has been implicated in Alzheimer's disease. The underlying mechanism associated with tau still remains unknown. Methods: Adult (6 to 8 months old) and Old (16 to 18 months old) mice overexpressing wild type human tau (Tg601 mice) were used. [18F]fluoro2deoxyDglucose ([18F]FDG) PET was taken without anesthesia. Voxel based SPM analysis was conducted to compare the images between age matched nonTg and Tg601 mice (N = 5) using SPM8 software. *Ex vivo* diffusion tenor (DT) MRI were performed using a 7 Tesla Biospec 70/16 MRI scanner . DT tractography was computed using the Diffusion Tooklkit and TrackVis software. Region of interest (ROI) analysis evaluated fractional anisotropy (FA), radial diffusibvity (RD), and axial diffusivity (AD) in the basal forebrain (vertical diagonal band of Broca [VDB], medial septum [MS] and horizontal diagonal band of Broca [HDB]). Acetylcholinesterase (AchE) activity and the amount of T, H and R transcripts of AchE mRNA were measured in 5 brain regions including the MS. The number of cholineacetyltransferase (ChAT) positive neurons in the basal forebrain will be quantified using the optical dissector method. Results: A SPM analysis of [18F]FDG PET revealed that hypometabolic areas appeared, involving the medial septum in adults and spread over the regions including hippocampal dentate gyrus. *Ex vivo* DT MRI tractography showed that the number of FA streamlines in the septohippocampal tract was lower in 3 old Tg601 mice than in 4 adult Tg601 mice (Figure). ROI analysis revealed that the FA value in the basal forebrain was significantly lower in old than in adult Tg601 mice while no significant difference in RD and AD values was detected. In old Tg601 mice, AchE activity and the amount of AchE mRNA T transcripts was higher exclusively in the septum. Conclusions: AchE upregulation in the septum may cause the selective degeneration of the septohippocampal cholinergic pathway in tauopathy model mice.



Disclosures: **Y. Motoi:** None. **Y. Hara:** None. **K. Hikishima:** None. **H. Mizuma:** None. **H. Onoe:** None. **S. Matsumoto:** None. **H. Okano:** None. **S. Aoki:** None. **N. Hattori:** None.

Poster

579. Tau in Cellular and Biochemical Models

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.07/C37

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Tau Consortium

AFTD

NINDS R21NS085487

Title: Tauopathy: Discovery of small molecule modulators of tau phenotypes in human iPSC-derived neuronal models of Frontotemporal Degeneration

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Abstract: Frontotemporal degeneration (FTD) disorders are characterized by progressive neuronal loss leading to dementia at a relatively young age and lack effective treatments to prevent its progression. Autosomal dominant forms of FTD are commonly associated with mutations in the MAPT gene encoding the Tau protein and characteristically exhibit potentially deleterious Tau protein aggregates in the frontal and temporal regions of the brain. With the goal of understanding the underlying pathology of FTD, identifying early disease markers, and identifying potential therapeutic targets, we have developed patient-derived, induced pluripotent stem cells (iPSCs) and differentiated neuronal cell models expressing a Tau variant associated with FTD (Tau-A152T). In this human neuronal cell model, independent clonal cell lines show, upon differentiation, rapid accumulation of Tau relative to control lines, both in hyperphosphorylated soluble, insoluble and high-molecular-weight protein forms, without differences in MAPT mRNA levels across lines. These data suggest that the accumulation of one or more particular Tau species is an early event in pathology preceding cellular toxicity and degeneration. Consequently, accumulation of Tau leads to reduced cellular resistance to specific stressors relevant to late onset neurodegeneration, including proteo-toxicity, excito-toxicity and mitochondrial function. To identify modifiers of Tau-associated phenotypes, we are pursuing the development of high-content, image-based assays that can support high-throughput screening of chemical libraries. A pilot screen in FTD patient iPSC-derived neuronal cells with known bioactive compounds, including FDA-approved or under clinical investigation, has revealed compounds targeting three main functional classes: autophagy protein clearance, neuronal signaling and the chaperone-protein folding pathways. Our lead compounds robustly downregulate steady-state levels of total and phosphorylated Tau, as well as insoluble Tau in neuronal cells, with less than a 24hr treatment. On-going studies are to further dissect modulation

of the folding and clearance pathways as a mechanism to alleviate Tau phenotypes associated with FTD and maintain protein homeostasis, including testing in iPSC-derived neurons from multiple families with Tau-P301L mutations. Collectively, we anticipate that this work will enable the discovery and validation of effective disease-modifying, targeted therapeutics, with relevance for a larger group of degenerative tauopathies and other dementias, such as Alzheimer's disease.

Disclosures: M. Silva: None. **C. Cheng:** None. **S. Reis:** None. **C. Tau:** None. **D. Lucente:** None. **B. Dickerson:** None. **S.J. Haggarty:** None.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.08/C38

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: IWT Grant 120492

Title: Synaptic contacts enhance cell-to-cell tau pathology propagation

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Abstract: Accumulation of insoluble Tau protein aggregates and stereotypical propagation of Tau pathology through the brain are common hallmarks of Tauopathies, including Alzheimer's disease (AD). Propagation of Tau pathology appears to occur along connected neurons, but whether synaptic contacts between neurons are facilitating propagation has not been demonstrated. Using quantitative *in vitro* models, we demonstrate that in parallel to non-synaptic mechanisms, synapses, but not merely the close distance between the cells, enhance the propagation of Tau pathology between acceptor hippocampal neurons and Tau donor cells. Similarly, in an artificial neuronal network using microfluidic devices, synapses and synaptic activity are promoting neuronal Tau pathology propagation in parallel to the non-synaptic mechanisms. Our work indicates that the physical presence of synaptic contacts between neurons facilitate Tau pathology propagation. These findings can have implications for "synaptic repair" therapies which may turn out to have adverse effects by promoting propagation of Tau pathology.

Disclosures: **S.C. Calafate:** Other; work is done under a research grant from the IWT, in collaboration with Janssen.. **B. de Strooper:** None. **J. de Wit:** None. **P. Vestreken:** None. **D. Moechars:** None.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: IDPH Grant 43282001B

Title: Tau45-230 forms neurotoxic aggregates in Alzheimer's disease and related disorders

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Abstract: We have previously shown that beta-amyloid-induced calpain activation leads to tau cleavage and the generation of the tau45-230 fragment in Alzheimer's disease (AD) and related disorders. In addition, the expression of this fragment in otherwise healthy hippocampal neurons induces neurodegeneration followed by cell death. More recently, we generated and characterized transgenic mice that express tau45-230 in pyramidal hippocampal neurons. The analysis of their phenotype showed enhanced neuronal death, synapse loss, and behavioral defects when compared to wild type controls. To get insights into the mechanisms underlying the neurotoxic effects of tau45-230, we have assessed its ability to aggregate in the context of these diseases. For these studies, brain samples obtained from AD and other tauopathy subjects were homogenized and Western blot analyses were performed under non-denaturing conditions. Homogenates of brain samples obtained from age-matched subjects were used as controls. Our results showed the presence of tau45-230 aggregates of ~68 and 168 kDa molecular weight, respectively, in all AD and other tauopathy brain samples analyzed. These aggregates differ in their susceptibility to sarkosyl. Thus, while most of the 168 kDa aggregates were sarkosyl-insoluble, only half of the 68 kDa ones remained after incubation with this detergent. We determined next to what extent tau45-230 aggregates are neurotoxic. For these experiments, recombinant tau45-230 was aggregated in the presence of arachidonic acid. Oligomeric tau45-230 was purified and added directly to the culture medium of hippocampal neurons. Seven days in culture hippocampal neurons were incubated in the presence or absence of these aggregates for 24 hrs and their morphology and viability were assessed. Our results showed that tau45-230 aggregates were incorporated into neurons and induced degeneration and cell death. Together,

these studies suggest that tau45-230 oligomers may play an important role in the mechanisms underlying neurodegeneration in AD and other tauopathies.

Disclosures: **A.B. Ferreira:** None. **A.E. Lang:** None.

Poster

579. Tau in Cellular and Biochemical Models

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Program#/Poster#: 579.10/C40

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Modifiers of tau oligomer internalization in human neurons derived from iPSCs

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Abstract: Neuronal inclusions of hyperphosphorylated and aggregated tau protein are a pathological hallmark of several neurodegenerative tauopathies, including Alzheimer's disease (AD). Increasing evidence suggest that tau pathology spreads throughout the brain via interconnected neurons, and that tau oligomers might be the transmitted pathogenic species. However, the molecular and cellular mechanisms of pathogenic tau transmission are not well established. We focused our research on defining the mediators of tau cellular internalization. Recently, it was suggested that cell-surface heparan sulfate proteoglycans (HSPGs) might play a role in tau cellular internalization. Our goal was to identify the specific molecular target within HSPGs that modifies tau uptake. We developed a model of tau oligomer internalization in human neurons derived from iPSCs, and performed a screen using lentiviral shRNAs to silence HSPGs. Internalized tau oligomers were detected based on fluorescent dye conjugated to tau protein. Here we present identified modifiers that clarify the involvement of HSPGs in tau internalization in a translatable model of human iPSC neurons. A better understanding of molecular mechanisms of tau internalization could lead to the discovery of novel therapeutic strategies that would inhibit tau pathology-spread and its consequences on neurodegeneration and cognitive dysfunction.

Disclosures: **M. Usenovic:** A. Employment/Salary (full or part-time):; Merck & Co., Inc. **S. Niroomand:** A. Employment/Salary (full or part-time):; Merck & Co., Inc. **J.J. Renger:** A. Employment/Salary (full or part-time):; Merck & Co., Inc. **S. Parmentier-Batteur:** A. Employment/Salary (full or part-time):; Merck & Co., Inc.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.11/C41

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: DoD/W81XWH-13-1-0253

Title: Exploring the molecular overlap in the brain and plasma of repetitive mTBI and AD mouse models using proteomic technology

Authors: *J. O. OJO;
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Abstract: Traumatic brain injury (TBI) is a major cause of disability in the military and civilian population, and for many years has been known to be a major risk factor for Alzheimer's disease (AD). Although the existence of this relationship is well recognized, and the overlap and distinction between pathological features of AD and repetitive mTBI, have long been the subject of reporting and discussion, the precise nature of how TBI leads to or precipitates AD pathogenesis is currently not understood. To address this problem we are generating time-dependent molecular profiles of response to repetitive mTBI and AD pathogenesis in mouse models, using proteomic analyses. We are using the well-validated hTau mouse models that develops age-related tau pathological features, and our well-established model of mTBI in C57BL/6 mice. Brain and plasma from these animals have been collected at different ages (for hTau mice), or at different timepoints after repetitive mTBI (C57BL/6). Liquid chromatography/mass spectrometry (LC-MS), in source collision induced dissociation (SCID) approaches and Tandem Mass Tag labeling technology are being applied to develop molecular profiles of proteins species that are significantly differentially expressed as a consequence of AD or mTBI. Generation of proteomic analyses are ongoing for comparisons of TBI profiles at 24hrs, 3, 6, 9 and 12 months post-injury with profiles at 3, 9 and 15 months of age in the hTau models. We anticipate that the exploration of molecular profiles from these animal models will enable us to identify cellular pathways that have pathogenic significance in human conditions. Moreover, we further aim to explore these identified pathways as potential targets for therapeutic intervention. **Key words:** mild traumatic brain injury, Alzheimer's disease, animal models, transgenic mice, proteomics. This study is funded by a CDMRP award to FC (DoD/W81XWH-13-1-0253), and by the Roskamp Foundation.

Disclosures: J.O. Ojo: None.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Conacyt 152535

Title: Overexpression of Tau protein induces a dispersion of the Golgi apparatus in neuroblastoma cells

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Abstract: Abnormal aggregation of Tau protein in the form of Paired Helical Filaments (PHF) is a pathological condition observed in hippocampal and cortical neurons of Alzheimer´s disease (AD) patients. Non-fibrillar aggregates of Tau are also observed in this pathology, however their pathological significance in the disease is still a debatable issue. Previously, we have probed that non-aggregated Tau causes morphological alterations in the nuclear architecture and plasma membrane blebbing when expressed in cultured neuronal and glial cells. In this study we further investigated whether Tau protein and several truncated Tau variants produce alterations in another membranous compartment, such as the Golgi apparatus. Cultured SH-SY5Y cells were transiently transfected with plasmids (pcDNA3.1Zeo(-)) containing the sequence for either full-length tau protein (Tau441) or several N- and C- termini truncated Tau variants. Cell morphology and protein expression were analyzed by immunofluorescence and confocal microscopy, and western-blotting analysis. After 48 hours of transfection, in 60% of the cells, Tau441 produced significant disruption of the Golgi ribbon structure into smaller elements dispersed from the narrow perinuclear area over the entire central part of the cell. Both Asp421 (Tau421) and Glu391 (Tau391) C-terminus truncated Tau variants produced similar results with no significant differences in the rate of Golgi dispersion. To evaluate the contribution of the N-terminus of Tau in the architecture and proper positioning of the Golgi apparatus in the cell, N-terminus truncated Tau constructs (Tau150-441; Tau123-391) were also expressed in SH-SY5Y cells. In accordance with other Tau variants, Tau150-441 and Tau123-391 also produced dispersion of this structure with no evidence of toxicity, as it was previously proposed. We also noticed that in the majority of the cells showing Golgi dispersion, a bundling effect of

microtubules was generated under the expression of either Tau441 or any truncated variant. These results may indicate that a mechanical force generated by Tau-induced microtubule bundling may be responsible for Golgi dispersion and that the repeated domain region of Tau is the main promoter of this effect

Disclosures: F. Garcia-Sierra: None. **F. Rodríguez-Cruz:** None. **F.M. Torres-Cruz:** None. **J. Escobar-Herrera:** None. **G. Basurto-Islas:** None.

Poster

579. Tau in Cellular and Biochemical Models

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 NS077239

NIH R01 AG032611

NIH R01 AG020197

Title: Tau antibody-mediated prevention of seeding of tau pathology and associated toxicity

Authors: *E. E. CONGDON[1], D. SHAMIR[2], H. R. B. SAIT[2], S. RASOOL[2], E. M. SIGURDSSON[3];
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Abstract: Tau pathology spreads between neurons in culture and *in vivo* and can be targeted with antibodies both intra- and extracellularly. We have developed 4E6G7, a monoclonal antibody recognizing pSer404 tau, and used it successfully in multiple models. Here we assessed its efficacy in preventing toxicity and spread of tau pathology mediated by paired helical filament (PHF) preparation from an Alzheimer's subject. Primary JNPL3 (P301L) neurons were incubated for seven days with PHF alone (1 or 10 μg/ml), PHF and 4E6G7 (10 μg/ml) added together (P + A), 4E6G7 added 24 h after PHF (P > A), or PHF added 24 h after 4E6G7 (A > P). PHF induced toxicity as measured by LDH (57% and 85% increase at 1 and 10 μg/ml, $p \leq 0.05$) and NeuN (31% and 94% decrease, $p \leq 0.004$). In P + A and P > A samples, this toxicity was prevented with readouts at control values, except for NeuN in the 10 μg/ml P > A group, which was significantly higher (116% control, $p = 0.02$), suggesting some neurotropic effect of the antibody. PHF exposure also increased neuronal tau levels in the remaining neurons at both

doses when normalized for NeuN (2.1- and 5 fold at 1 and 10 μg/ml, $p \leq 0.01$), which were significantly reduced in both the P + A, and P > A groups ($p \leq 0.006$ - 0.0006), to (1 μg/ml) or somewhat higher (10 μg/ml, 1.5- and 1.2 fold, $p \leq 0.01$) than control values. PHF also increased the ratio of pSer199/NeuN (1.1- and 5 fold, $p \leq 0.02$) which was reduced to control values at both doses in both P + A and P > A groups. To ascertain whether antibody efficacy required internalization, we tested the P + A and P > A paradigms using microscopy and inhibitors of antibody uptake. In the P + A group, PHF and 4E6G7 formed extracellular complexes. In P > A cells, PHF was taken up by neurons, and 4E6G7 colocalized with it. Using an endocytosis inhibitor, we found that blocking 4E6G7 uptake had no effect on efficacy in the P + A group. In contrast, in P > A cells, blocking 4E6G7 uptake significantly reduced its protective effects (68% NeuN loss, $p = 0.00005$). Additional neurons were grown in microfluidic chambers (JNPL3 on one side, WT on the other) to assess the effect of 4E6G7 on PHF spread. PHF was added to the JNPL3 side, and 72 h later 24% of the WT cells contained labeled PHF material. The P + A group had significantly fewer positive cells (14%, $p = 0.01$), and the P > A group showed a strong trend towards reduced transmission (18% positive, $p = 0.06$). These data suggest that multiple mechanisms are occurring, and that both extracellular blockage and promotion of intracellular clearance are valid methods for preventing seeding of tau pathology and associated toxicity. Antibodies that can affect both pathways are likely to be more efficacious than those acting only within one compartment.

Disclosures: **E.E. Congdon:** None. **D. Shamir:** None. **H.R.B. Sait:** None. **S. Rasool:** None. **E.M. Sigurdsson:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; H. Lundbeck A/S. F. Consulting Fees (e.g., advisory boards); H. Lundbeck A/S.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.14/C44

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH R01 NS077239

NIH R01 AG032611

NIH R01 AG020197

Title: Antibodies targeting truncated tau protein reduce tau pathology in primary neuronal and mixed cortical cultures

Authors: S. R. MODAK[1], M. SOLESIO[1], S. KRISHNASWAMY[1], E. E. CONGDON[1], *E. M. SIGURDSSON[2];
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Abstract: Truncation of the tau protein at aspartate in position 421 (Asp421) is a characteristic feature of tauopathies such as Alzheimer's disease, and may have a role in their pathogenesis. Tau immunotherapy targeting various epitopes is a promising approach to treat these diseases. In this study, we investigated, in primary neuronal and mixed cortical cultures, the therapeutic potential of two monoclonal antibodies with high (5G2A3, 10^{-9} M) and low (1G11A10, 10^{-6} M) affinity for the free Asp421 epitope. The cultures derived from day 0 JNPL3 (P301L) mice were pretreated with paired helical filament (PHF) enriched preparation (1 μg/ml) from an Alzheimer's brain for 24 h, then washed and incubated with antibody (10 μg/ml) for further 24, 48, 72 and 96 h. Subsequently, western blots were conducted for phospho- and total tau protein to determine if the antibodies could clear PHF derived/induced tau proteins from the cultures. The higher affinity Asp421 antibody led to significant and sustained reduction in both phospho- (up to 87% at 96 h, $p<0.001$) and total tau (up to 54% at 96 h, $p<0.0001$) in the mixed culture, compared to control IgG which had no effect. This tau antibody had as pronounced effect in the primary neurons at 24 and 48 h (phospho-tau: 89% reduction at both time points, $p<0.001$; total tau: 58% at 24 h, $p=0.001$ and 45% at 48 h, $p=0.005$) that subsided a bit at the later time points (phospho-tau: 75% reduction, $p=0.003$ at 72 h and 68% reduction at 96 h, $p=0.008$; total tau: 6% reduction, $p>0.05$ at 72 h and 43% reduction, $p=0.006$ at 96 h). The lower affinity Asp421 antibody was less efficacious in reducing phospho- and total tau (up to 49% reduction at 96 h, $p<0.0001$ and 36% reduction at 96 h, respectively, $p<0.0001$) in the mixed cortical culture, and was ineffective in the primary neuronal culture to reduce either phospho- or total tau. In conclusion, this study clearly shows: 1) the therapeutic potential of targeting tau protein truncated at Asp421; 2) that higher affinity antibody against this particular epitope is more efficacious, and; 3) that greater efficacy is observed in mixed cortical cultures than in primary neurons, presumably because of contribution from phagocytic microglia that promote degradation of tau-antibody complexes. Neurons in mixed cultures are also healthier and, therefore, likely to be better suited to clear/degrade such complexes.

Disclosures: S.R. Modak: None. **M. Solesio:** None. **S. Krishnaswamy:** None. **E.E. Congdon:** None. **E.M. Sigurdsson:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; H. Lundbeck A/S. F. Consulting Fees (e.g., advisory boards); H. Lundbeck A/S.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

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Topic: C.02. Alzheimer's Disease and Other Dementias

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NIH R01 AG020197

NIH 8 T32 MH 96331-2

NIH 1 T32 NS 69514-1

Title: Tau antibodies reduce tau levels in differentiated but not in non-differentiated human SH-SY5Y cells

Authors: *D. B. SHAMIR[1], E. M. SIGURDSSON[2];
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Abstract: Our laboratory has pioneered targeting pathological tau proteins for clearance with immunotherapies. To further clarify the mechanism of action of tau antibodies, we have been using SH-SY5Y human neuroblastoma cells among other models. These cells take up tau antibodies, which co-localize within the endosomal-lysosomal system. To create a more physiological system we have differentiated our naïve SH-SY5Y cells using retinoic acid and brain derived neurotropic factor (BDNF), and characterized them using western blot analysis. As expected, the differentiated cells have greater total tau protein compared to non-differentiated cells (172%, p=0.025, n=7-8). Incubation for 24 hours with different tau antibodies to the S396/404 tau region led to reduction in total tau levels in differentiated (19-25%; p=0.004, n=15-16) but not in non-differentiated cells, compared to controls. Interestingly, during this 24 hour period, the differentiated cells took up less tau antibodies than their non-differentiated counterparts (45% vs. 83%; p<0.0001, n=8-12). Clathrin-mediated endocytosis inhibitor (Dynasore, 5 ug/ml), reduced antibody uptake by 39% in the differentiated cells (p=0.03, n=7) but had no effect in non-differentiated neurons (n=4). Measurement of tau levels are in progress. However, with our flow cytometry protocol we demonstrated that antibody uptake can blocked in non-differentiated cells with a bulk-mediated endocytosis inhibitor (Cytochalasin D, 1-10

ug/ml, 31-55% reduction, $p<0.0001$, $n=2$). In prior publications we have shown that antibody uptake in primary mouse neuronal cultures is mainly through clathrin-mediated endocytosis (~80%), and to a lesser extent (~20%) via bulk-mediated endocytosis (Congdon EE et al, JBC, 288, 2013). Our current findings indicate that differentiated culture models may be needed to determine the therapeutic efficacy of tau antibodies, but non-differentiated culture models may be useful to focus exclusively on the bulk-mediated pathway. However, the physiological relevance of such non-differentiated models is more limited as higher antibody uptake did not translate to greater efficacy compared to differentiated cells. Future studies will seek to clarify how antibody-mediated tau clearance pathways may differ in these two models.

Disclosures: D.B. Shamir: None. **E.M. Sigurdsson:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; H. Lundbeck A/S. F. Consulting Fees (e.g., advisory boards); H. Lundbeck A/S.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Ohio University SEA Grant

Ohio University OURC Grant

Title: Alzheimer’s disease cellular model: 2,2’-dithiodipyridine-induced Tau oligomerization in primary rat cortical neurons

Authors: C. QIAN[1], K. L. KRAUS[1], *R. A. COLVIN[2];
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Abstract: The self-assembly of microtubule-associated protein Tau is recognized as one of the primary hallmarks of Alzheimer’s disease (AD), which destabilizes micro-tubule (MT) assembly and facilitates formation of “prion-like” Tau oligomers. So far, the cellular models mimicking Tau aggregation are either based on genetic manipulations of several domains of Tau protein, or by application of high concentrations of chemicals that oxidize cysteines on Tau, forming an intermolecular disulfide bridge. However, a cellular model is lacking that shows controllable,

visible and quantifiable oligomerization of endogenous Tau in primary neurons. Tau self-assembly in rat primary cortical neurons was induced by applying the thiol oxidant 2,2'-dithiodipyridine (DTDP). Both immunofluorescent microscopy (IF) and immunoblotting (WB) using an antibody to total Tau were utilized to observe and quantify DTDP-induced Tau oligomerization. Immunofluorescent results showed that DTDP-induced Tau aggregation was both dose- and time-dependent. Treating cells with 10, 30, 60, or 100μM DTDP caused increased Tau IF of 114±10%, 195±24%, 178±28% and 275±29% in cell bodies; 110±5%, 139±3%, 123±2% and 166±17% in neurites, and 83±19%, 205±36%, 269±41% and 529±12% increase in Tau aggregates, respectively (mean ± SE, n=3). Treating cells with 30μM DTDP for 5, 15, 30, or 60min caused increased Tau IF of 124±13%, 166±19%, 200±40% and 222±12% in cell bodies; 104±11%, 127±7%, 115±8% and 152±22% in neurites, and 104±11%, 127±7%, 115±8% and 152±22% increase in Tau aggregates, respectively (mean ± SE, n=3). WB showed that incubating culture extracts with DTT reduced the detectable levels of high MW oligomers and dimers and DTT increased the levels of Tau monomers. This suggests that the self-assembly of Tau protein induced by DTDP was most likely attributable to intermolecular disulfide bond formation between cysteine residues on repeat domains of Tau. DTDP is well known to release zinc from zinc binding proteins, therefore, zinc chelator TPEN was tested on the DTDP-induced model. 100μM TPEN partially but significantly reduced the number of Tau aggregates induced by either 60μM or 100μM DTDP. These data show the pivotal role of intermolecular disulfide bond formation in shifting the balance toward assembly-prone conformations, increasing substantially the rate of formation of intracellular Tau aggregates. This research reveals an effect of increased intracellular free zinc in the process of Tau aggregation.

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Poster

579. Tau in Cellular and Biochemical Models

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH NS076117

Belfer Neurodegeneration Consortium

Title: The role of selective autophagy in neurofibrillary tangle pathology

Authors: *Y. XU, H. ZHENG;
Baylor Col. of Med., Houston, TX

Abstract: Tauopathies consist of a group of diseases, including frontotemporal dementias and the most common form Alzheimer's disease, and are characterized by the accumulation of intracellular neurofibrillary tangles (NFTs) composed of aggregates of hyperphosphorylated Tau protein and extensive neurodegeneration. Tau is normally localized to the neuronal axons where it binds and stabilizes the microtubules. Aberrant Tau phosphorylation leads to its dissociation from the microtubules followed by aggregation and redistribution to cell bodies and dendrites. Accumulating evidence has implicated impaired autophagy-lysosome pathway in neurodegenerative diseases including diseases of tauopathies. In this study, we examined the role of the autophagy receptor protein p62/SQSTM1 in tauopathy. We found that p62 is significantly increased in neurons of tau transgenic mouse models. Using a seeding based cell model in which tau aggregates can be induced by seeding with tau transgenic brain lysates, we found that overexpression of p62 specifically decreased insoluble tau while knockdown of p62 increased insoluble tau, suggesting that selective p62-dependent autophagy counteracts tangle pathology.

Disclosures: Y. Xu: None. **H. Zheng:** None.

Poster

579. Tau in Cellular and Biochemical Models

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: FONDECYT 1140968

Title: Pathological forms of tau affects mitochondrial dynamics in Alzheimer´s disease

Authors: *R. A. QUINTANILLA, K. VERGARA, F. A. CABEZAS-OPAZO;
Inst. de Ciencias Biomédicas, Univ. Autónoma de Chile, Lab. of Neurodegenerative Dis., Santiago, Chile

Abstract: Accumulative evidence suggests that tau pathology and Aβ aggregates affects the neuronal function compromising energy supply and antioxidant response in Alzheimer´s disease (AD). Several reports have suggested that in AD, the mitochondria could be affected in terms of bioenergetics, transport, and dynamics. Defects in mitochondrial dynamics are related to changes in mitochondrial fission/fusion proteins, and previous evidence suggests that tau pathology could

affect this process. In this context, we analyzed the effects of pathological forms of tau on mitochondrial dynamics in neuronal cells and primary cortical neurons. In these studies, we expressed tau in the pseudo-phosphorylated form at S396/404 (T42EC) and caspase-cleaved tau (T4C3), and we evaluated changes in mitochondrial morphology using Mito-mCherry. Expression of T42EC did not induce significant changes in mitochondrial morphology compared to GFP and full-length tau. However, T4C3 and both pseudo-phosphorylated and caspase-cleaved tau (T42EC-C3) expression induced significant mitochondrial fragmentation, compared to cells that expressed full-length tau. Interestingly, concomitant with the mitochondrial fragmentation the neuronal cells that expressed T4C3 and T42EC-C3 presented an enhanced mitochondrial depolarization and superoxide production after treatment with Aβ fibrils. In addition, complementary studies were made in immortalized cortical neurons that expressed same constructs of tau to evaluate the expression of mitochondrial fission (Drp-1/Fis1) and fusion (Mitofusins 1, 2 (Mfn1, 2)/Opa1) proteins. Expression of T4C3 and T42EC-C3 significantly decreased total Drp-1 levels with no apparent effects in Opa1, Mfn1, and Mfn2. In contrast, full-length (T4) and pseudo-phosphorylated tau (T42EC) expression did not affect mitochondrial fission/fusion proteins expression in immortalized cortical cells. These observations are consistent with the mitochondrial morphology studies that showed an evident mitochondrial fragmentation in neuronal cells that expressed truncated and pseudo-phosphorylated tau. Altogether these findings indicate that the presence of pathological forms of tau affects mitochondrial dynamics and that this alteration could contribute to Aβ toxicity in neurons.

Disclosures: **R.A. Quintanilla:** None. **K. Vergara:** None. **F.A. Cabezas-Opazo:** None.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.19/C49

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant NS073899

VA Grant BX001637

Title: Regulating proteostasis to control both normal and pathological tau biology

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Abstract: Chaperone proteins play an important role in identifying and correcting the proper conformation of proteins. Thus, the relationship between the microtubule associated protein tau and chaperones is unusual simply because tau is a disease-associated intrinsically disordered protein (IDP) that lacks a defined structure. Of particular interest is the interaction between tau and the constitutively expressed Hsp70 (Hsc70), as Hsc70 plays a number of important roles in the cell and also stabilizes tau levels. We have evidence that this stabilization of tau by Hsc70 can facilitate its pathogenesis in various ways. However, isoform selective Hsc70 inhibitors have not yet been developed. As proof-of-concept, we determined that a functionally inactive variant of Hsc70 facilitated tau clearance via the proteasome in brain, exactly mimicking what we predict selective inhibition of this Hsp70 isoform would cause. We determined that an altered interactome was responsible for tau clearance caused by this Hsc70 variant. Of note, this inactive Hsc70 variant recruited tubulin proteins compared to wildtype Hsc70, suggesting a role for Hsc70 activity in microtubule regulation. Indeed, using live cell imaging, Hsc70 facilitated microtubule assembly but only when it was active and surprisingly only when tau was present. In particular if Hsc70 activity was disrupted, microtubules were disrupted. In this way, active Hsc70 uses tau as a co-chaperone to regulate microtubule dynamics. Thus chronic treatment with an Hsc70 inhibitor would facilitate microtubule injury and cytotoxicity, but we found that taking a chemotherapeutic approach using intermittent dosing still promoted tau clearance without damaging microtubules. This suggests that strategies to restore the proteostasis network can be effectively used to treat disease when used in a regimen similar to that used for some chemotherapies and contraceptives.

Disclosures: **S.N. Fontaine:** None. **M.D. Martin:** None. **C.A. Dickey:** None.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.20/C50

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Pentobarbital-induced hypothermia modulates total and phosphorylated tau: implication of alpha7 nicotinic receptors

Authors: ***A. GOBERT**, F. IOP, V. PASTEAU, K. ALBINET, L. DANOBER, C. LOUIS, P. LESTAGE;
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Abstract: Background In Alzheimer's Disease (AD) and other tauopathies, paired helical filaments are described to be enriched in hyperphoshorylated tau proteins. Previous studies have shown that anaesthesia-induced hypothermia promotes extensive tau hyperphophorylation at various epitopes (Planel et al., 2007). The present study aimed at deciphering the role of α_7 nicotinic acetylcholine receptors (α_7nAChR) and the efficacy of central acting α_7 nicotinic ligands in inhibiting tau phosphorylation. **Method** Hypothermia was induced in wild-type (WT) male C57Bl/6J and α_7nAChR knock-out (KO) mice using pentobarbital injections. After ninety minutes, animals were sacrificed and whole brain extracts prepared. Total tau and phospho (pSer202, pThr181, pSer262, pSer396 and $pThr^{231}$) tau, as well as $GSK_{3\beta}$ and phospho $GSK_{3\beta}$ were quantified using an ELISA technique (MesoScale Discovery's electrochemiluminescence detection). In parallel, Western blot analyses were performed using different total and phospho tau antibodies. **Results** After anaesthesia-induced hypothermia total tau levels and its phosphorylation at Ser396 were decreased, while an increase in phosphorylation at Ser202 and Thr181 was detected using the ELISA technique. No significant changes were observed at the levels of Thr231 and Ser262 phosphorylation of tau and neither on $GSK_{3\beta}$ nor phospho GSK_3. In contrast, Western blot analyses, did not detect any changes in total tau levels, independent of the antibody used. Ser396 levels did not change neither. In accordance with the observation using ELISA detection, Western blot analyses revealed an increase of phosphorylation at the Ser202-Thr205 and the Thr181 epitopes, while at Thr231 no change could be detected. Hypothermia-induced changes in total or phosphorylated tau were not attenuated in α_7nAChR KO mice as compared to WT mice. Likewise, acute administration of α_7nAChR agonists, S24795 (3 mg/kg, ip) and ABT107 (0.3 mg/kg, ip), 30 min before pentobarbital did not influence hypothermia-induced alteration of total and phosphorylated tau levels. **Conclusions** Anaesthesia-induced hypothermia in wild-type mice results in changes at different phosphorylation sites of tau. Similar observations were made in α_7nAChR KO mice and after administration of two α_7nAChR agonists, suggesting that α_7nAChR do not play a critical role in hypothermia-mediated tau phosphorylation. All procedures using the animals conformed to the European Directive 2010/63/EU, and its adaptation to French law (décret 2013/118), on the protection of animals used for scientific purpose. Planel E., et al. The Journal of Neuroscience, 27(12): 3090-3097, 2007

Disclosures: **A. Gobert:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **F. Iop:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **V. Pasteau:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **K. Albinet:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **L. Danober:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **C. Louis:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier. **P. Lestage:** A. Employment/Salary (full or part-time):; Institut de Recherches Servier.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.21/C51

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH NS41073

NIH MD007599

PSC-CUNY 67851-00 45

The Graduate Center, City University of New York

Title: The effects of manipulating the de-ubiquitinating enzymes USP14 and UCH-L1 on the levels of TAU and polyubiquitinated proteins: relevance to Alzheimer's disease

Authors: *M. J. KIPROWSKA[1,2], A. STEPANOVA[3,4], A. GALKIN[3], M. FIGUEIREDO-PEREIRA[1];
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Abstract: Impairment of the ubiquitin/proteasome pathway (UPP) plays an important role in Alzheimer Disease (AD) as indicated by the accumulation of ubiquinated and oxidized proteins detected in the AD brains. The accumulation of toxic aggregates in AD brains is attributed, in part, to UPP dysfunction, which occurs very early in the neurodegenerative cascade. Thus to enhance protein degradation by the UPP prior to aggregate formation could be a highly effective therapeutic approach to prevent/delay neurodegeneration in AD. A proposed strategy for promoting protein degradation by the UPP is inhibiting USP14. This deubiquitinase disassembles polyubiquitin chains potentially delaying degradation of proteasomal substrates. We assessed the protective efficacy of inhibiting USP14 pharmacologically with IU1 and genetically with siRNA, in rat cortical neurons treated with prostaglandin J2 (PGJ2). PGJ2 is an endogenous mediator of inflammation that induces the accumulation of ubiquitinated (Ub)-proteins. Firstly, we observed that high IU1 concentrations (HIU1, >25μM) blocked Ub-protein accumulation induced by PGJ2, while low IU1 concentrations (LIU1, ≤25μM) had no impact. In addition, HIU1 by itself or in combination with PGJ2 induced (a) neurotoxicity and (b) calpain-dependent cleavage of Tau, caspase and spectrin. Secondly, we established that HIU1 decreased ATP levels and inhibited mitochondrial complex I. Consequently, HIU1 blocked E1-mediated ubiquitin-activation and 26S proteasome assembly, which are energy-dependent processes. These data support that HIU1 prevents Ub-protein accumulation, in part, by blocking E1-dependent

ubiquitin-activation thus halting ubiquitination. Thirdly, we showed that USP14 knockdown by siRNA failed to promote Ub-protein degradation in neurons treated with PGJ2. Finally, we demonstrated that PGJ2 inhibits E1-activity, but still induces accumulation of Ub-proteins. These Ub-proteins are likely to be formed prior to and stabilized by the PGJ2-treatment. Accordingly, PGJ2 inhibits deubiquitinases like UCH-L1, thus potentially stabilizing polyUb-chains. In conclusion, both IU1 and PGJ2 diminish E1 activity. However, IU1 blocks Ub-protein accumulation, while PGJ2 promotes it. The contrast between the IU1- and PGJ2-impact on Ub-protein accumulation, could be related to the mechanism by which the targeted deubiquitinases destabilize polyUb-chains. In conclusion, a better understanding of the mechanisms by which distinct deubiquinases regulate the levels of polyUb-chains is critical for drug development to reduce the accumulation of aberrant proteins in neurodegenerative diseases such as AD.

Disclosures: M.J. Kiprowska: None. **A. Stepanova:** None. **A. Galkin:** None. **M. Figueiredo-Pereira:** None.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.22/C52

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Center for Translational and Basic Research (CTBR)

Title: Tau phosphorylation plays a role in mRNA 3' end processing

Authors: F. E. KLEIMAN[1], J. E. BAQUERO[1], M. ORDONEZ[1], *A. ALONSO[2,1];
[1]Hunter Col., City University of New York, NY; [2]Deaprtment of Biol., Col. of Staten Island, CUNY, Staten Island, NY

Abstract: Tau is a microtubule-associated protein involved in a number of neurodegenerative disorders, including Alzheimer's disease (AD). In normal individuals, Tau is a highly soluble, non-phosphorylated protein that stabilizes microtubules in the cytoplasm of neurons. However, neurons in AD's contain insoluble hyperphosphorylated-tau aggregates known as paired helical filaments. Previous studies have shown that Pin1, a prolyl-isomerase initially identified as a mitotic regulator overexpressed in most human cancers, is involved in the regulation of Tau phosphorylation under different conditions. Furthermore, Tau has been functionally linked to another Pin1 substrate, the tumor suppressor p53 and some of its isomers. Interestingly, Dr. Kleiman's lab identified p53 as an activator of PARN-dependent mRNA deadenylation in the

nucleus as part of the DNA damage response. As Pin1, p53 and PARN are localized in the nucleus and are involved in the regulation of mRNA 3' end processing under different cellular conditions, we hypothesize that Tau might also localize in the nucleus of non-neuronal cells and functionally overlap with these factors. Our cellular fractionation assays with samples of HCT116 human colon carcinoma cell line indicated that tau isoforms are present in the cell nucleus. Interestingly, nuclear isoform patterns of Tau changed upon Pin1 inactivation, UV irradiation, p53 expression and/or phosphatase treatment. Using co-immunoprecipitation assays, we showed that some Tau isoforms can form (a) complex(es) with p53, Pin1 and PARN, and these interactions change under different cellular conditions. Strikingly, overexpression of Tau, but not of its phosphomimic mutants, induces nuclear deadenylase activity in CHO cells. Finally, siRNA-mediated knockdown of Tau decreases nuclear deadenylation in samples from HCT116 cells under non damaging conditions. Moreover, Tau knockdown further increases the previously described UV-induced deadenylation. Although more research is necessary, these preliminary results reveal a new potential role for Tau in the regulation of mRNA 3' processing. These findings also support the idea that factors involved in cancer and Alzheimer's disease might play a role in regulating gene expression by a functional interaction with the mRNA 3' processing machinery in different conditions, resulting in specific gene expression patterns.

Disclosures: F.E. Kleiman: None. **J.E. Baquero:** None. **M. Ordonez:** None. **A. Alonso:** None.

Poster

579. Tau in Cellular and Biochemical Models

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.23/C53

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant EY022358

Title: Phosphorylated tau has increased binding affinity to dynactin

Authors: *S. D. CRISH[1], W. J. GELDENHUYS[1], C. M. DENGLER-CRISH[1], G. N. WILSON[2];
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Abstract: Hyperphosphorylation of the microtubule-associated protein tau plays a major role in driving pathology in neurodegenerative conditions such as Alzheimer's disease (AD). In its normal phosphorylation state, tau acts to organize and stabilize the cytoskeleton in axons

whereas hyperphosphorylation reduces tau's affinity for microtubules. After tau disassociates from microtubules, it then "falls back" to the somatodendritic compartment where it forms neurofibrillary tangles that characterize AD. Both the loss of tau-mediated microtubule organization as well as abnormal translocation and aggregation of tau in non-axonal compartments negatively impact neuronal structure and function, leading to neurodegeneration. While much is known about tau's phosphorylation state influencing microtubule binding, little is known about the mechanism of tau translocation to the soma. Using co-immunoprecipitation techniques, we report here that phosphorylation of recombinant tau isoforms by glycogen synthase kinase 3-beta (GSK-3β) increases tau's affinity for dynactin - a major component of the retrograde axon transport machinery. Our data suggest that phosphorylation of tau causes it to bind to the retrograde molecular motors which transport it to the soma.

Disclosures: S.D. Crish: None. **W.J. Geldenhuys:** None. **C.M. Dengler-Crish:** None. **G.N. Wilson:** None.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant AG026249

The Massachusetts Life Sciences Foundation

Title: Tau phosphorylation correlates with cellular tau uptake

Authors: *S. TAKEDA[1], S. L. DEVOS[1], S. WEGMANN[1], C. COMMINS[1], C. K. NOBUHARA[1], A. D. ROE[1], I. COSTANTINO[1], R. PITSTICK[2], G. A. CARLSON[2], M. P. FROSCH[1], B. T. HYMAN[1];
[1]Neurol., Massachusetts Gen. Hosp., Charlestown, MA; [2]McLaughlin Res. Inst., Great Falls, MT

Abstract: Background Cognitive deficits in Alzheimer's disease (AD) are most closely linked with the progression of neurofibrillary tangles (NFTs) in a hierarchical pattern. Although the precise mechanisms for this characteristic tau pathology spread remain unknown, accumulating evidence suggests a transsynaptic transfer of the pathological form of tau between neurons. We previously found that high-molecular-weight (HMW) tau can be the endogenous form of tau involved in tau uptake and propagation. Here, we examined the role of phosphorylation in

cellular tau uptake. Methods Cellular tau uptake was assessed using FRET-based HEK-tau-biosensor cells (Holmes BB et al. PNAS 2014) or mouse primary neurons treated with brain-derived tau. Brain extracts (PBS soluble fraction) from a tau-transgenic mouse model (rTg4510, 12 months old) or human AD postmortem tissue (frontal cortices from five cases with Braak stage VI) were used to treat cells. Results First, we examined the effect of tau dephosphorylation on cellular uptake. Lambda phosphatase treatment dephosphorylated tau in rTg4510 brain extract without changing HMW tau levels; this resulted in a reduction of tau uptake in HEK-tau-biosensor cells. We then assessed tau uptake from phospho-tau-immunodepleted rTg4510 brain extract in primary neurons. Eight different phospho tau epitope specific antibodies (pS199, pT205, pS262, pS369, pS400, pS404, pS409, and pS422) were used for the immunodepletion. Phospho-tau-specific antibodies were less efficient at immunodepletion than the total tau antibody (HT7); however, some phospho-tau antibodies (pS199, pT205, and pS396) more efficiently reduced the neuronal tau uptake than did the total tau antibody. This suggests that they specifically interacted with a species of tau important for uptake. We then examined uptake efficiency of brain-derived tau from five different AD cases in HEK-tau-biosensor cells and found a positive correlation between uptake efficiencies and phospho-tau levels. Conclusions Three lines of data support the idea that phosphorylation is important for neuronal tau uptake: (i) enzymatically dephosphorylating the HMW tau blocks uptake; (ii) some phospho-tau-specific antibodies are able to block uptake; and (iii) uptake efficiency correlates with the extent of phosphorylation in biological samples. These observations indicate that phosphorylation may enhance cellular tau uptake.

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Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.25/C55

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: IWT140773

Title: Functional analysis of AD-derived paired-helical filaments in cellular and *in vivo* Tau aggregation models

Authors: A. MARREIRO[1], K. VAN KOLEN[2], M. BORGERS[2], D. VAN DAM[3], M. MAHIEU[2], G. DANEELS[2], M. VANDERMEEREN[2], R. WILLEMS[2], K. DE WAEPENAERT[2], I. VAN DE WEYER[2], P. P. DE DEYN[3], L. TEMMERMAN[1], G. DEPUYDT[1], L. VER DONCK[2], A. EBNETH[2], L. SCHOOFS[1], J. KEMP[2], *M. H. MERCKEN[2];
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Abstract: Objectives: Although several studies demonstrate that Tau aggregates can be transmitted from neuron to neuron, little information is available on the mechanism of spreading and on the molecular properties of the Tau seed. The aim of this study is to identify and characterize pathological species of Tau capable of transmitting pathology. **Methods:** Aggregates were isolated from *post mortem* AD and transgenic mice (male PS19 and female P301S) brain tissue. Biochemical characterization was done by Western blotting (reducing and non-reducing), SEC, ELISA and AlphaLisa. Aggregates were then evaluated in both cellular and *C. elegans* aggregation models and *in vivo* Tau injection models. **Results:** Biochemical analysis revealed that total and sarcosyl insoluble fractions from both AD derived material and transgenic animals contain Tau aggregates capable of triggering aggregation in a cellular model. When PHFs are injected in the cortex of P301L mice (mixed gender), Tau pathology (confirmed by native PAGE, Western Blot and IHC) is observed from one to three months after injection in injected and non-injected hemispheres. **Conclusions:** This study further characterized the molecular properties of PHFs and demonstrated that *in vitro* seeding capacity correlated with aggregate load. Injection experiments in Tau transgenic mice show that purified PHFs can trigger Tau aggregation *in vivo*. Confirmation of this seeding effect in a *C elegans* model is currently ongoing. Further injection studies with fractionated AD brain samples are needed to get more insight in the molecular properties of this type of seed.

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Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.26/C56

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: The Alzheimer's Drug Discovery Foundation

The Cullen Trust

The Mitchell Center for Neurodegenerative Disease

Title: The specific targeting of tau oligomers therapeutically in Alzheimer's disease

Authors: *R. KAYED[1], D. L. CASTILLO-CARRANZA[2], J. E. GERSON[3], M. GUERRERO-MUNOZ[2], U. SENGUPTA[2], B. HAWKINS[4], A. BARRETT[5];
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Abstract: The majority of neurodegenerative tauopathies are associated with the pathological accumulation of additional amyloid proteins, notably amyloid-β in Alzheimer's disease (AD). Studies have shown that intermediate aggregates known as oligomers are the most toxic species in disease. The common toxic factor in these diseases, the tau oligomer, is a promising therapeutic target in mixed pathology diseases. We have recently shown that passive immunotherapy with a novel tau oligomer-specific antibody is effective in two different pure tauopathy models, P301L and Htau mice. Here we directly test the interaction between tau and amyloid oligomers and the efficacy of anti-tau oligomer immunotherapy in a model of AD. We have evaluated brain tissue and oligomers derived from AD patients for the interaction between amyloid proteins and tau using biochemical and immunohistochemical analysis with our novel oligomer-specific antibodies. To investigate the efficacy of immunotherapy with anti-tau oligomer monoclonal antibody (TOMA) in an AD model, we examined the behavior and pathology of treated Tg2576 mice. We found that Aβ oligomers can seed the aggregation of tau *in vitro* and are colocalized in disease, forming hybrid oligomers. Treatment with TOMA reverses cognitive detriment and decreases tau oligomer levels in Tg2576 mice, while increasing stable Aβ plaque levels. Our results suggest that oligomeric Aβ has a synergistic relationship with tau oligomers. This combined with passive immunotherapy results suggest that tau oligomers are a good therapeutic target in AD and potentially in other mixed pathology tauopathies. **Supported by:** The Alzheimer's Drug Discovery Foundation, The Cullen Trust and the Mitchell Center for Neurodegenerative Diseases.

Disclosures: **R. Kayed:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Has patent applications on the compositions and methods related to tau oligomers and antibodies. **D.L. Castillo-Carranza:** None. **J.E. Gerson:** None. **M. Guerrero-Munoz:** None. **U. Sengupta:** None. **B. Hawkins:** None. **A. Barrett:** None.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

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Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Fluorescent assays for the detection of beta-Amyloid and Tau modification enzymes: Pin1 and Glutaminyl cyclase

Authors: O. GURINOVICH, *C.-Y. KO, X. WANG, R. ZHANG, V. RAKHMANOVA; AnaSpec, Inc. EGT Group, Fremont, CA

Abstract: Alzheimer’s disease (AD) is one of the most common neurodegenerative diseases that lead to dementia. Hallmark of AD is the presence of senile plaques and neurofibrillary tangles in the affected brain. It is believed that senile plaques originate due to the aggregation of beta-Amyloid (Aβ) peptides while neurofibrillary tangles are caused by the accumulation of hyperphosphorylated Tau proteins. Both, Aβ and Tau, can undergo different modifications during cellular trafficking that may affect their aggregation properties. Thus, it is important to identify what enzymes can modify these two AD biomarkers and study modifying agents in more details. Glutaminyl cyclase, also known as Glutaminyl-peptide cyclotransferase (QPCT), and Peptidyl-prolyl *cis-trans* isomerase NIMA-interacting 1 (Pin1) are such enzymes which modify Aβ and Tau respectively. Pin1 catalyzes *cis/trans* isomerization of the phosphor-Serine/Threonine-Proline peptide bond of Tau protein. This leads to the Tau dephosphorylation and prevents it from forming neurophibrilary tangles. On the contrary, QPCT can catalyze production of pyroglutamic beta-amyloid peptides that aggregate much faster compared to the unmodified ones and may produce senile plaques at higher rate. In order to investigate properties of these two protein modifying enzymes, reliable assays for Pin1 and Glutaminyl cyclase activities have to be developed. We have designed two assays to detect activity of Pin1 and QPCT enzymes using fluorescent based peptide substrates. Both assays use long-wavelength green fluorophore that is released after enzyme and developer action and can be monitored at Ex/Em=490/520nm. Pin1 catalyzes change of fluorescent substrate into *trans* form that is

cleaved by the substrate developer and releases fluorophore much faster compared to the unmodified *cis* substrate. Thus, intensity of the fluorescent signal can be correlated with Pin1 activity in a sample. For the Glutaminyl cyclase assay, substrate is converted into the pyroglutamate form that is readily cleaved by the assay developer and generates green fluorescence. Both assays have sensitivity in nanogram range. QPCT assay was validated with human saliva and cerebrospinal fluid. Inhibitors for both assays were selected to ensure that they act on enzymes only and do not affect developer. Homogeneous format of both assays is ideal for inhibitors screening during drug discovery.

Disclosures: O. Gurinovich: A. Employment/Salary (full or part-time):; AnaSpec, Inc. EGT Group. **C. Ko:** A. Employment/Salary (full or part-time):; AnaSpec, Inc. EGT Group. **X. Wang:** A. Employment/Salary (full or part-time):; AnaSpec, Inc. EGT Group. **R. Zhang:** A. Employment/Salary (full or part-time):; AnaSpec, Inc. EGT Group. **V. Rakhmanova:** A. Employment/Salary (full or part-time):; AnaSpec, Inc. EGT Group.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

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BrightFocus A2013364S

Title: Differential recognition of pathological forms of tau protein with N-terminal antibodies in tauopathies and *in vitro* assays

Authors: *B. COMBS, K. K. COX, C. HAMEL, N. M. KANAAN;
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Abstract: Tauopathies are characterized by the aggregation of tau protein and extensive neurodegeneration. Traditionally, several phosphoepitope-specific antibodies were used to observe tau neuropathology, but these markers do not indicate whether tau is in potentially toxic conformations. Recent work has shown that during the early development of tau pathology the protein undergoes conformational changes leading to aberrant exposure of the N-terminus. This region contains a phosphatase-activating domain that initiates a PP1-GSK3 signaling cascade resulting in disruption of anterograde fast axonal transport. Impaired axonal transport can facilitate synapse loss, axonal degeneration and ultimately neurodegeneration. Thus, antibodies that recognize the N-terminus of tau are uniquely positioned to detect early tau pathology and identify forms of the protein that may exert toxic effects on the cell. We have characterized several N-terminal antibodies to determine their specific epitopes and relative abilities to bind pathological tau in numerous tauopathies and *in vitro* assays. We found that small changes in the epitope can greatly affect antibody reactivity with recombinant tau monomers or aggregates, tau pathology in various human tauopathies, and rodent tau. Three of the antibodies displayed significantly greater affinity for aggregated tau than for monomeric tau while others had similar affinities for both forms of the protein in sandwich ELISAs. The differences in reactivity for monomeric and aggregated tau samples were absent in denaturing assays (e.g. Western blotting), indicating that some of these N-terminal antibodies identify pathological conformational states of the protein. The antibodies displayed differential abilities to detect canonical pathology in Alzheimer's disease, progressive supranuclear palsy, Pick's disease, corticobasal degeneration, and chronic traumatic encephalopathy. The antibodies that recognize conformational exposure of the N-terminus labeled early pre-tangle inclusions in neurons. These results indicate that some N-terminal antibodies are useful in identifying pathological species of tau in human disease as well as in *in vitro* assays. Moreover, conformational changes leading to exposure of the N-terminus occur early in disease progression and the differences observed from minor variations in epitopes suggest subtle differences in the conformation of the N-terminus exist in disease-related forms of tau.

Disclosures: **B. Combs:** None. **K.K. Cox:** None. **C. Hamel:** None. **N.M. Kanaan:** None.

Poster

579. Tau in Cellular and Biochemical Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 579.29/C59

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: DFG (SFB944, project P1)

Title: Regulation of RNA protein granule formation and tau mRNA expression by G3BP1

Authors: *R. BRANDT, F. SÜNDERMANN, M. IGAEV, B. NIEWIDOK, A. PEREIRA DA GRACA, L. BAKOTA;
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Abstract: RNA protein (RNP) granules play an important role in translational regulation and mediating mRNA stability. This may be also important for regulating the expression of the microtubule-associated protein tau, which is translated from different mRNA variants and is causally involved in tauopathies. We have previously reported that RNP granules modulate tau isoform expression and induce neuronal sprouting suggesting a morphoregulatory function of RNP granule formation during neuronal development and disease (Moschner et al. (2014) J. Biol. Chem. 289:16814-25). Ras-GAP Src homology 3 domain-binding protein 1 (G3BP1) is highly expressed in neurons, is present in stress granules, and may play an important role in granule formation and organization. G3BP1 is a multivalent phosphoprotein that contains four low complexity (LC) regions, which may play a role in nucleating RNP granules and mediating interactions with other cellular components. Here we addressed the question, whether LC regions and phosphorylation of specific residues in G3BP1 are involved in RNP granule formation and function. We prepared a panel of G3BP1 deletion constructs with different numbers of LC regions and phosphomimicking and phosphoblocking mutants. We developed a quantitative live cell imaging assay to analyze the dynamics of the interaction of photoactivatable GFP (PAGFP)-tagged G3BP1 constructs with RNP granules by fluorescence decay after photoactivation (FDAP) measurements. We report that G3BP1 interacts with RNP granules in a highly dynamic fashion. We show that the activities of G3BP1 to nucleate RNP granules and to interact with granules are mechanistically distinct, require different numbers of LC regions, and are modulated by phosphorylation and stress conditions. We demonstrate that regulation of tau expression requires the activity of G3BP1 to induce the formation of RNP granules. The data indicate that regulation of tau mRNA expression by G3BP1 requires the formation of RNP granules, that RNP granule formation is driven by the presence of multiple LC regions, and modulated by phosphorylation of G3BP1. Modulation of G3BP1 activity and dynamics may provide a new approach to influence tau expression in tauopathies such as Alzheimer's disease.

Disclosures: R. Brandt: None. **F. Sündermann:** None. **M. Igaev:** None. **B. Niewidok:** None. **A. Pereira da Graca:** None. **L. Bakota:** None.

Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 580.01/C60

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Investigating the role of copper deficiency and zinc in a mouse model of late onset Alzheimer's disease

Authors: *S. N. HOWELL, K. N. BOGGS, J. M. FLINN;
Psychology, George Mason Univ., Fairfax, VA

Abstract: This study examines the roles of zinc (Zn) and copper (Cu), in a mouse model of late onset Alzheimer's disease (AD). Previous research has shown that excess Zn causes behavioral impairments in rats and mice; these impairments were remediated by the addition of copper to the Zn-enhanced water.This information suggests that excess Zn may be causing impairments through an induced Cu deficiency. To test this theory directly, we initially raised mice modeling early onset AD (hAPP; Swedish and Indiana mutations) on specialized Cu control and Cu deficient diets that differed only in levels of Cu (created with Harlan laboratory nutritionists). The results of that study implied that 1.) the effects of Cu and Zn may differ in the brain regions controlling different behaviors, and that 2.) the effect of enhanced Zn may not be entirely due to an induced Cu deficiency. Currently, we aim to explore this unexpected interaction further in a late-onset AD model. Specifically, we are interested in mice carrying the E4 allele of the APOE gene, which constitutes a high risk factor for development of AD, with some evidence showing that it may be protective early on. Male hAPP transgenic (Tg) mice were crossed with homozygous ApoE4 females to obtain a cross that models late onset AD. There are six groups (wildtype (Wt) and late-onset mice on (a.) lab water + Cu control diet, (b.) lab water + Cu deficient diet, or (c.) Zn-enhanced water + Cu control diet). Open field and odor habituation/dishabituation, Morris water maze (MWM) (spatial learning/memory) and sociability tasks are being assessed at 6 and 12 months of age allowing for examination of the potential early protective effects of the ApoE4 gene and identification of dietary interactions in early and late stages of the disease. Six month pilot open field data shows a significant interaction between genotype and diet (ApoE4, Cu deficient mice show the greatest distance traveled and the greatest velocity). All animals show normal odor habituation/dishabituation. Preliminary MWM pilot data indicates that, at 6 months, Wt and ApoE4 mice do not differ in latency across days. However, there is a trend towards a day X diet interaction, with Cu control mice showing faster latencies across days, as compared to the Cu deficient group. This study extends the examination of dietary effects to multiple types and stages of AD. This may identify specific dietary interactions that may be playing a role, since results in our early onset AD model differed from those in other studies that used diets with differing metal levels or metal ratios, such as the Cu/Zn ratio, and in non-nutritive substances, such as soy and phytates.

Disclosures: **S.N. Howell:** None. **K.N. Boggs:** None. **J.M. Flinn:** None.

Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 580.02/C61

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: APP/APOE4 mice show impaired nest building and circadian rhythm activity at 6 months

Authors: *J. M. FLINN, K. N. BOGGS, J. L. MINGOS, P. KAKALEC, S. N. HOWELL; Psychology, George Mason Univ., Fairfax, VA

Abstract: Mutations in certain genes are known to increase the likelihood of developing Alzheimer's disease (AD). While there are genetic risk factors associated with late onset AD, because of it's sporadic nature, it appears as though a combination of genetics and environmental factors likely play a role in development of AD after age 65. One known genetic risk factor for developing late onset AD is the presence of the ε4 allele of the ApoE gene, which is present in 40% of late-onset cases (National Institutes on Aging, 2015). Circadian rhythms (CR) and activities of daily living (ADL) become disrupted in Alzheimer's disease. Sundown syndrome or "sundowning" is a common circadian rhythm disturbance observed in patients with AD, which causes increased confusion and agitation in the evening, trouble sleeping, and altered levels of activity throughout the day (Cipriani, et al., 2015). Circadian rhythm activity can be measured in Alzheimer's mouse models by assessing their wheel running behavior. Activities of daily living in humans include behaviors such as bathing, dressing, and feeding. ADL behaviors can be observed in mice by using a simple nest construction assay*, which capitalizes on the natural tendency of mice to construct nests. The present study utilizes a mouse model of AD possessing both the APP mutation and the E4 allele to assess CR and ADL at 6 months. Preliminary data looking at nest construction in 6 month wildtype C57/6J mice (n=14) and APP/E4 mice (n=7) using shredded paper revealed significant impairment in nest building behavior in APP/E4 mice ($p<.01$); no significant difference was observed between males (n=6) and females (n=15). Preliminary data also suggests circadian rhythm irregularities in APP/E4 mice on a variety of CR measures such as bouts per day, which were higher in APP/E4 animals compared to wildtypes ($p<.01$). A difference in onset of activity between APP/E4 and WT animals was trending, and began earlier in the evening for WT animals ($p= .058$). Offset of activity was significantly different between APP/E4 and WT animals with a later offset for WT animals ($p < 0.01$). Specifically, wildtype animals begin their wheel running activity about an hour before E4 animals, and ended their activity an hour later than E4 animals. A sex difference was observed in these animals, with females having a longer average bout length compared to males ($p < 0.01$),

more counts per bout than males ($p < 0.01$), and a higher average peak rate than males ($p < 0.01$). In general, this suggests that females have increased overall activity compared to males. Future analyses will include additional data for 6 month animals, in addition to 9 and 12 month data.

Disclosures: J.M. Flinn: None. **K.N. Boggs:** None. **J.L. Mingos:** None. **P. Kakalec:** None. **S.N. Howell:** None.

Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 580.03/C62

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Impact of human APP overexpression on cerebral cholesterol metabolism in ApoBxAPP and APPSL mice

Authors: *C. SCHWEINZER[1], T. LOEFFLER[1], E. STEYRER[2], B. HUTTER-PAIER[1], M. WINDISCH[3];
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Abstract: Besides the focus on Aβ and Tau in Alzheimer's disease (AD), it is increasingly evident that other pathologic incidents, such as vascular pathologies, are associated with AD. Also lipids, especially cholesterol, are discussed to contribute to AD pathogenesis. Several studies showed that cholesterol impacts on APP metabolism and vice versa. Additionally, elevated plasma cholesterol in midlife is associated with an increased risk for AD. Interestingly, in mice overexpressing human apolipoprotein B-100 (ApoB-100) it was shown, that changes in the plasma lipid composition alone lead to cognitive decline at higher ages. To see whether this phenotype could be induced earlier by additional cholesterol uptake, a high-fat feeding study was conducted with animals overexpressing human ApoB-100 and/or human APPSL. ApoBxAPP, ApoB-100, APPSL and wild type (WT) mice, received either a standard chow or high-fat-diet (HFD) for 3 months. At an age of 6 months, all animals underwent several behavioral tests, including the Morris water maze task (MWM). Changes in cholesterol content and mRNA levels of cholesterol metabolism-associated genes were measured in cortices of all mice. While behavioral performance was not influenced by HFD, reduction of cortical free cholesterol levels and mRNA expression patterns under normal diet and HFD conditions in human APP overexpressing mice argue for an important role of APP in cerebral lipid metabolism From our

results we conclude that increased APP metabolism in ApoBxAPP and APPSL mice induces mechanisms to reduce free cholesterol levels.

Disclosures: C. Schweinzer: None. **T. Loeffler:** None. **E. Steyrer:** None. **B. Hutter-Paier:** None. **M. Windisch:** None.

Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 580.04/C63

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH AA021517

Title: "Fatty Brain" resulting from altered ApoE expression following pubertal binge ethanol consumption in rats

Authors: *A. ASIMES[1], M. M. PRZYBYCIEN-SZYMANSKA[2], T. R. PAK[2];
[1]Cell and Mol. Physiol., [2]Loyola Univ. Chicago, Maywood, IL

Abstract: Apolipoprotein E (ApoE) is a carrier protein necessary for the delivery of cholesterol from astrocytes to neurons. ApoE mRNA expression and activity can be altered with alcohol exposure. Alcohol consumption among adolescents often occurs in a binge-like pattern, where the blood alcohol concentration (BAC) is raised above 0.08% in 2 hours, and can lead to various neurological and cognitive health risks in adulthood. These long-term consequences may be mediated by stable epigenetic modifications to the genome, also making them transferable to offspring. We tested the hypothesis that adolescent binge alcohol exposure decreases ApoE expression and function in the brain, leading to a "fatty brain" phenotype. Wistar rats were administered a repeated binge-EtOH exposure paradigm at early and late puberty (PND37, 67). They received 3g/kg of 20% (v/v) EtOH via oral gavage daily for 3 days, then 2 days vehicle and another 3 days EtOH. Animals were paired for mating 24h after the last EtOH dose, with pairs consisting of all combinations of EtOH- and vehicle-treated males and females. Litters were culled to 10 pups per dam and were left until PND7 when all animals were euthanized. The hypothalamus was extracted and both DNA and RNA were isolated. Primary astrocyte cultures were prepared from cortical tissue of both pups and parents (PND103). We found a decrease in ApoE mRNA expression in the hypothalamus of adult males exposed to EtOH, but no difference was measured in females. Correspondingly, there was an increase in cholesterol accumulation in cortical astrocytes of binge-EtOH exposed males compared to vehicle treated counterparts, but

there was no change in females. In the EtOH-naïve offspring of EtOH-exposed parents, we also found downregulation of ApoE in the hypothalamus. These results suggest that EtOH-induced downregulation of ApoE results in a decrease in astrocytic secretion of lipids, leading to “fatty astrocytes” and cholesterol-starved neurons.

Disclosures: **A. Asimes:** None. **M.M. Przybycien-Szymanska:** None. **T.R. Pak:** None.

Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 580.05/C64

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: ApoE4 impairs brain insulin signaling and glucose metabolism

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Abstract: Diabetes and impaired insulin signaling in the brain have been linked to the pathogenesis of Alzheimer’s disease (AD). Epidemiological studies show that diabetic patients are at higher risk for AD. Levels of insulin, insulin receptor, and insulin signaling are lower in AD brains than normal individuals. The ε4 allele of the apolipoprotein E (*APOE*) gene is the strongest genetic risk factor for late-onset AD, whereas the ε2 allele is protective. Interestingly, the association between diabetes and amyloid pathology is particularly strong among *APOE4* carriers. In addition, recent clinical trials revealed that intranasal insulin administration significantly improves the cognitive function of AD patients in a manner that depends on *APOE* genotype. *APOE4* carriers, either as healthy adults or with dementia, have lower cerebral glucose metabolism in FDG-PET studies. Despite these observations in humans, the mechanism by which apoE isoforms differentially regulates brain insulin signaling and glucose metabolism remain unclear. Here we report apoE isoform-dependent glucose metabolism and insulin signaling pathways in mouse models. Specifically, we found that cerebral blood flow is reduced in apoE4-targeted replacement (TR) mice starting at a young age compared with apoE3-TR mice. Furthermore, aged apoE4-TR mice have reduced capacity to metabolize cerebral glucose compared to apoE3-TR mice upon glucose challenge when examined by *in vivo* microdialysis. The levels of glucose transporters, insulin receptor and signaling were significantly decreased in aged apoE4-TR mice. Finally, overexpression of apoE4 in astrocytes in a novel mouse model further suppressed insulin signaling. Our study provides novel insights into the pathogenic mechanisms of apoE4 and insulin resistance in AD, and suggests therapeutic strategies to

ameliorate abnormal insulin signaling and glucose metabolism in an apoE isoform dependent manner.

Disclosures: N. Zhao: None.

Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 580.06/C65

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH P01AG030128-06

Title: Age effects on apoE lipidation in EFAD mice and human brain samples

Authors: *R. M. SALZMAN, S. GHURA, K. P. KOSTER, N. C. COLLINS, C. SMITH, L. M. TAI, M. LADU;
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Abstract: The ε4 allele of the apolipoprotein (APOE) gene is the greatest genetic risk factor for Alzheimer's Disease (AD), while increased amyloid-β (Aβ42) causes familial AD. The soluble oligomeric aggregates of Aβ (oAβ) are recognized as a likely proximal neurotoxin. ApoE functions in the transport of lipid within the central nervous system (CNS). Lipid and cholesterol are added to apoE-containing lipoprotein particles by ATP-binding cassette transporters A1 and G1 (ABCA1/G1). Studies comparing brains of EFAD mice (5XFAD mice expressing human APOE) demonstrate that apoE in E4FAD mice is less lipoprotein associated/lipidated compared to E2FAD and E3FAD mice at 2-, 4- and 6 months. However, apoE lipoprotein-association/lipidation levels have not been measured in EFAD mice over 6 months of age. Thus, we hypothesize that with age, Aβ pathology increases anf apoE lipidation decreases. The goal of the current study is to determine apoE levels and apoE lipidation in 10-, 14-, and 18 month E2FAD, E3FAD and E4FAD mice. To confirm results from the transgenic EFAD mice, we measured apoE lipidation in AD versus control human subjects with APOE3/3, APOE3/4 and APOE4/4. A 3-step sequential protein extraction protocol, which facilitates the release of apoE from lipoproteins in the detergent fraction (TBS + 1% Triton X-100), was utilized to quantify lipoprotein-associated apoE (TBSX-apoE). ApoE levels in each fraction were measured by ELISA to produce an apoE extraction profile. In addition, TBS and TBSX fractions were analyzed by native gels. As well, levels of ABCA1 and ABCG1 were measured by Western blots. Results demonstrate that with age in the EFAD mice and AD status in human subjects,

apoE lipidation levels decreased (APOE4 > APOE3). In parallel, the levels of ABCA1/G1 protein were also decreased. Thus, data from both the EFAD mice and human brain samples provide evidence that apoE-lipidation state is one mechanism by which APOE4 may contribute to AD risk. Further, our data suggests that ABCA1/G1 may be important therapeutic targets to increase the lipidation of particulalry apoE4.

Disclosures: **R.M. Salzman:** None. **S. Ghura:** None. **K.P. Koster:** None. **N.C. Collins:** None. **C. Smith:** None. **L.M. Tai:** None. **M. LaDu:** None.

Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 580.07/C66

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Alzheimer's Association Grant IIRG-10-172459

NIH-funded KU Alzheimer's Disease Center Grant P30AG035982

KU New Faculty Start-up Funds

Title: Female and male sex hormones differentially regulate apolipoprotein J (ApoJ) in primary neurons

Authors: *S. K. WOODY, A. CHHIBBER, L. ZHAO;
Univ. of Kansas Sch. of Pharm., Lawrence, KS

Abstract: Alzheimer's disease (AD) is currently one of the most feared neurodegenerative diseases affecting over 5.4 million Americans. Though extensively studied, the molecular mechanisms that trigger the onset of AD are not completely understood nor has an effective treatment been developed. Therefore, before a treatment strategy is established, it is imperative that the field focuses on the identification of risk mechanisms that would allow for targeted prevention, risk reduction, or early intervention in the preclinical phase of AD. Apolipoprotein J (ApoJ), also known as clusterin, is a multi-functional chaperone protein shown to reduce Aβ42 aggregation and increase Aβ42 clearance. Recently, ApoJ has been highlighted by two independent genome-wide association studies that demonstrated a significant association between ApoJ variants and the development of late-onset AD (LOAD). Additionally, several studies have shown increased ApoJ expression in AD brain; however reduced ApoJ expression has been associated with aging and ApoJ polymorphisms. ApoJ is currently the third most

significant genetic risk factor for the development of LOAD, however the neurophysiological roles of ApoJ are largely unknown. Our recent analyses have demonstrated that ApoJ expression is significantly reduced in female brain with early aging; a time period that corresponds with a significant and irreversible decline in ovarian hormone levels. Additionally, our data indicate that the interaction between ApoJ and insulin-like growth factor 1 (IGF1) serves as a central contributor to the overall decline in energy metabolism in the early aging female brain. Led by these findings, we hypothesize that sex and sex hormones differentially regulate ApoJ expression in the brain and a deficiency in ApoJ expression negatively impacts brain metabolism in a sex dependent manner. In these studies we have conducted a set of experiments to determine the modulation of ApoJ by sex hormones in primary hippocampal and cortical neurons. These data present a possible mechanism by which sex and sex hormones differentially impact the etiology of AD; specifically, these data provide an essential foundation for understanding how the triad of sex and sex hormones, ApoJ, and brain metabolism regulate each other to modulate the risk for LOAD.

Disclosures: **S.K. Woody:** None. **A. Chhibber:** None. **L. Zhao:** None.

Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 580.08/C67

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH 5R01AG033007-05

NIH 5T32NS007098-34

Title: Effects of ApoE isoforms on learning and memory in knock-in mice expressing the Danish dementia BRI2 mutant

Authors: *K. ISHIWARI, F. BIUNDO;
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Abstract: Alzheimer’s disease (AD) is the most common neurodegenerative disorder among the elderly and characterized by progressive neuronal loss and dementia. Familial AD is caused by mutations that alter the proteolytic processing of amyloid β precursor protein (APP). Three major isoforms of apolipoprotein E (ApoE) exist in humans, ApoE2, ApoE3, and ApoE4, of which ApoE4 is the major genetic risk factor for late-onset familial and sporadic AD, although the

mechanism by which ApoE4 affects the pathogenesis of the disease is unclear. Familial Danish Dementia (FDD) is a neurodegenerative disorder caused by a mutation in the BRI2/ITM2b gene, whose protein product BRI2 inhibits APP processing. The FDD mutation results in loss of BRI2, leading to enhanced APP processing and the consequent release of potentially toxic APP metabolites. FDD and AD share clinical and neuropathological features. Moreover, BRI2/ITM2b has been identified as one of the candidate regulatory node genes predicted to mediate the common patterns of gene expression shared by healthy ApoE4 carriers and late-onset AD patients not carrying the ApoE4 allele (Rhinn et al., 2013), suggesting that FDD and AD have common pathogenic mechanisms. We generated a knock-in mouse model of FDD (FDDKI). FDDKI mice carry one mutant and one wild-type BRI2 allele, which is genetically congruous with the human pathology. FDDKI mice exhibit reduced long-term potentiation in the hippocampus and age-dependent memory deficits. The present study was conducted to examine how the FDD mutation might interact with ApoE isoforms in the regulation of cognitive functions and behavior. To that end, FDDKI mice were crossed with human ApoE targeted replacement mice, in which the mouse ApoE gene was replaced with either the human ApoE3 or ApoE4, and the resultant male mice of the F2 generation of four genotypes (ApoE3+/+, FDDKI/ApoE3+/+, ApoE4+/+, FDDKI/ApoE4+/+; n=16-25 per genotype) were assessed longitudinally for learning and memory at 4, 6, 12, and 16-17 months of age using a battery of tests including the Morris water maze and the Y-maze. The results showed that mice carrying the ApoE4 allele displayed working/short-term spatial memory deficits relative to mice carrying the ApoE3 allele starting in early middle age, while long-term spatial memory of ApoE4+/+ mice was not adversely affected even at 16-17 months, and that the FDD mutation impaired working/short-term spatial memory in mice carrying the ApoE3 allele and produced impaired long-term spatial memory in mice carrying the ApoE4 allele in middle age. The present results suggest that the FDD mutation may differentially affect learning and memory in ApoE4 carriers and non-carriers.

Disclosures: **K. Ishiwari:** None. **F. Biundo:** None.

Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 580.09/C68

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH 1R01AG041971-01A1

Title: ApoE dependent interactions of the α-secretase ADAM10 in Alzheimer's disease

Authors: *B. SHACKLETON[1,2], C. BACHMEIER[1,2], F. CRAWFORD[1,2];
[1]Roskamp Inst., Sarasota, FL; [2]The Open Univ., Milton Keynes, United Kingdom

Abstract: The ApolipoproteinE4 (apoE4) isoform is the strongest genetic risk factor for developing Alzheimer's disease (AD). While the exact mechanism in which apoE influences AD pathology is unknown, it has been associated with excessive Amyloid β (Aβ) deposition in the AD brain. Aβ is produced from the Amyloid Precursor Protein (APP) following sequential cleavage by the β- and γ-secretase enzymes. Alternatively, APP can be processed by the α-secretase, A Disintegrin And Metallo proteinase domain containing protein 10 (ADAM10). This protein exists as both a membrane bound and soluble protein (sADAM10) and results in the formation of the neurotropic soluble APPα from APP. Much of the focus in the field has been directed at potential therapeutics targeting the β-and γ-secretases. However, these approaches have yet to yield significant clinical improvements with several disappointing phase 3 trials. Here, we investigate the influence of apoE on the α-secretase pathway as a potential modulatory mechanism of AD pathology. In a cell free assay we observed apoE isoform and dose dependent effects on ADAM10 activity. This was supported by *in vitro* experiments showing apoE isoform dependent production of sAPPα in whole cells. To evaluate the impact of apoE on ADAM10 in the human population, we examined cortical brain tissue from control and AD subjects stratified by APOE genotype. No significant differences in ADAM10 expression or activity were detected in whole brain homogenate. However, significant apoE isoform and disease state differences in sADAM10 were detected in the soluble brain fraction. More specifically, sADAM10 levels are highest in apoE4/4 control samples compared to the other apoE genotypes. This interaction is not evident in the AD samples where the levels of sADAM10 remain low and static. The apoE isoform also effects the ability of sADAM10 to cleave substrate independent of the disease state (apoE2>apoE3>apoE4). This results in an interaction where the lower the activity of sADAM10, the higher the levels. However, this interaction appears to be lost in the AD samples. We hypothesise that this inverse correlation functions as a protective feedback mechanism to compensate for the reduced sADAM10 activity due to the apoE isoform present. In conclusion, this study demonstrates an isoform-specific influence of apoE on APP processing, which may provide a novel strategy for reducing ab burden in the AD brain.

Disclosures: **B. Shackleton:** None. **C. Bachmeier:** None. **F. Crawford:** None.

Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 580.10/C69

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant 20131205

Title: Unraveling the role of apolipoprotein E in age- and Abeta-related neuronal dysfunction

Authors: *J. A. KLICKSTEIN[1], K. KUCHIBHOTLA[2], L. WROBLESKI[1], S. WEGGMAN[1], M. ARBEL-ORNATH[1], E. HUDRY[1], B. T. HYMAN[1];
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Abstract: Background: Impairment in synaptic plasticity and neuronal integrity are observed both in "normal" aging and Alzheimer's disease (AD), albeit to different magnitudes. Previous studies suggest that apolipoprotein E (apoE), the main lipoprotein carrier in the central nervous system, may be an important molecular modulator of both processes. Interestingly, the absence of apoE in mice has been shown to cause cognitive deficits, while the same genetic alteration alleviates amyloid pathology in AD transgenic models, thus eventually conferring a beneficial outcome in the disease. Using novel *in vivo* methodological approaches, this study aims to further our understanding of how apoE modulates resilience and susceptibility of the neural system in both physiological and pathological contexts. Results: Using *in vivo* calcium imaging in the visual cortex of awake animals, our preliminary results suggest that apoE disruption impairs neuronal tuning for the direction of visual stimuli in adult wild-type (Wt) mice (8-10 months), resulting in an increased proportion of broadly tuned cells and a decreased number of highly tuned responders. This functional impairment is further amplified in APPPS1 AD transgenic mice when compared with Wt; however, the absence of apoE in those mice tends to improve this particular phenotype (the percentage of highly tuned cells in APPPS1/APOEKO animals reaches similar levels as APOEKO). The orientation selectivity index, however, remains unchanged between all the experimental groups. Interestingly, the global amount of Aβ and the density of diffuse amyloid aggregates were not significantly different in APPPS1 and APPPS1/APOEKO mice (even though a lower amount of dense-core fibrillar deposits was observed), therefore emphasizing the role of apoE in modulating Aβ-related neuronal dysfunction rather than an effect on amyloid deposition. In aged mice (18 month old), the presence of a higher percentage of "off-responders" was observed in APPPS1 compared with Wt, APOEKO and APPPS/APOEKO animals, demonstrating that impairment of neuronal function may be specifically associated with the overexpression of AD-related genes and can be compensated by the absence of apoE. Conclusion: These results argue in favor of a complex role of apoE in maintaining neuronal function in a normal brain while alleviating amyloid-associated impairment of neuronal activity in aged transgenic mice. Further investigation of the synaptic profile of these different mouse lines will allow us to precisely associate our *in vivo* observations

in awake animals with changes in the distribution of pre- and post-synaptic elements, as well as changes in apoE-Aβ interactions.

Disclosures: J.A. Klickstein: None. **K. Kuchibhotla:** None. **L. Wrobleski:** None. **S. Weggman:** None. **M. Arbel-Ornath:** None. **E. Hudry:** None. **B.T. Hyman:** None.

Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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the Alzheimer’s Association and Cure Alzheimer’s Fund

Title: APOE2 protects against age-related memory decline: a clinical and pre-clinical evaluation

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Abstract: Objective: Apolipoprotein E (apoE), a major cholesterol carrier in the brain, is associated with a strong risk for Alzheimer’s disease. Compared to the risky APOE4 gene allele, the effects of the protective APOE2 gene allele are vastly understudied, and thus, need to be further clarified. Methods: We reviewed National Alzheimer’s Coordinating Center (NACC) clinical records and performed preclinical experiments using human apoE-targeted replacement (apoE-TR) mice, which do not show amyloid pathology. Results: Clinically, APOE2 allele protects against age-related cognitive decline. This effect is more prominent in homozygous carriers of APOE2, and is also seen in subjects without amyloid pathology. APOE2 especially protects against memory function decline. In animal studies, aged apoE2-TR mice also exhibited

preserved memory function in the water maze tests. Regardless, apoE2-TR mice showed similar or greater age-related changes in synaptic loss, neuroinflammation and oxidative stress compared to apoE3- or apoE4-TR mice. However, apoE concentrations in the cortex, hippocampus, plasma and cerebrospinal fluid (CSF) were positively correlated with memory performance across apoE isoforms, where apoE2-TR mice had higher apoE levels. More interestingly, apoE2-TR mice exhibited the lowest levels of cholesterol in the cortex, irrespective of higher levels in CSF and plasma. The cholesterol levels in the brain and CSF were oppositely associated with apoE levels and memory performance across apoE isforms. Interpretation: APOE2 protects against age-related memory decline independently of age-related synaptic/neuroinflammatory changes and amyloid accumulation, while apoE and its-associated cholesterol metabolism might contribute to this protective effect.

Disclosures: **M. Shinohara:** None. **T. Kanekiyo:** None. **J. Fryer:** None. **G. Bu:** None.

Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

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Program#/Poster#: 580.12/C71

Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Impaired interaction between apolipoprotein E and Alzheimer’s disease-associated mutation in TREM2

Authors: *Y. ATAGI[1], X. CHEN[2], C.-C. LIU[1], H. ZHENG[2], X. LI[1], C. VERBEECK[1], N. SAKAE[1], P. DAS[1], S. YOUNKIN[1], J. FRYER[1], G. BU[1];
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Abstract: Rare heterozygous mutations in the triggering receptor expressed on myeloid cells 2 (TREM2) have been identified as risk factors for number of neurodegenerative diseases such as late-onset Alzheimer’s disease (LOAD), Parkinson’s disease (PD), and frontotemporal dementia (FTD). TREM2 is a type I transmembrane receptor that is expressed in the cells of myeloid origin such as macrophage and osteoclast. In the central nervous system (CNS), it is expressed in the microglia, the resident immune cells of the CNS. TREM2 signals through its adaptor protein DAP12 to promote phagocytosis of apoptotic cells and to suppress the secretion of pro-inflammatory cytokines. Homozygous mutations in TREM2 or DAP12 result in Nasu-Hakola disease which is characterized by frontal dementia with multifocal bone cysts. It is believed that disease-linked mutations in TREM2 are loss-of-function mutations as many of them are clustered around putative ligand binding domain. The fact that some of the mutations also result in non-

functional truncated proteins or disrupt TREM2-DAP12 association further supports the loss-of-function pathway. Although phospholipids, HSP60, LPS, and other polyanionic molecules have been suggested to bind TREM2, the physiological ligand of TREM2 in the CNS has not yet been identified. Here, we show that apolipoproteins bind to TREM2 in biochemical assays. Apolipoproteins are a class of proteins that bind to lipids and form lipoproteins. Among different apolipoproteins, apoA1, apoE, and clusterin (apoJ) are found in the CNS, and apoE and clusterin are secreted by astrocytes. Of note, the ε4 allele of the APOE gene which encodes apoE4 is the strongest genetic risk factor for LOAD, and a SNP in clusterin has also been associated with risk of LOAD. In addition, all three apolipoproteins found in the CNS have been shown to play roles in inflammatory response. In this study, we show that apoA1, apoE, and clusterin bind specifically to extracellular domain of TREM2. ApoE preferentially binds to the surface of apoptotic neurons and promotes phagocytic uptake by microglia in a TREM2-mediated manner. More interesting, LOAD-linked TREM2 variant R47H shows significantly reduced binding to apoE. Our data suggest that loss-of-function in ligand binding might be a contributing mechanism underlying the association between TREM2 mutations and impaired microglial function in removing apoptotic cells or abnormal protein aggregates in neurodegenerative diseases. This study shed a light in the role of TREM2 in the CNS and suggests strategies to target TREM2-related neuroinflammatory pathways to treat neurodegenerative diseases.

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Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: FONDECYT 1140473

Title: Effects of cholesterol and GM1 on the membrane actions of Amyloid beta in hippocampal neurons

Authors: ***E. FERNANDEZ**[1], F. J. SEPULVEDA[1], C. OPAZO[2], L. G. AGUAYO[1];
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Abstract: Introduction The ability of beta-amyloid peptide Aβ to disrupt the plasma membrane through formation of pores and membrane breakage has been previously described, but the mechanism and molecular determinants for these effects are largely unknown. Therefore, we examined if the association and subsequent membrane perforation induced by Aβ was dependent on GM1 and cholesterol levels. **Results** The results showed that either decreasing cholesterol or increasing GM1 facilitated membrane perforation. For example, pretreatment of hippocampal neurons with MβCD significantly decreased the membrane levels of cholesterol (fluorescent-punctas/20μm: control=18±2 vs. MβCD=10±1, $p<0.05$). This was accompanied by a decrease in Aβ clustering at the membrane (Aβ fluorescent-punctas/20μm, control=37±3 vs. MβCD=23±3, $p<0.01$). Interestingly, membrane perforation with Aβ occurred much faster when the cholesterol content was diminished (time to establish perforated configuration (TEPC): control=8±2 vs. MβCD=2.3±0.5 min, $p<0.01$), suggesting that the presence of cholesterol in the membrane can modulate the distribution and the membrane perforation by Aβ. On the other hand, increasing GM1 by liposome facilitated the membrane perforation (TEPC: control=15±1 vs. GM1=6±1 min, $p<0.05$). Additionally, using Cholera Toxin Subunit-B (CTB) to block the interaction of Aβ with GM1, we found that membrane perforation was significantly attenuated. Furthermore, pretreatment with CTB decreased the membrane association of Aβ (fluorescent-punctas/20μm, Aβ: control=14±2 vs. CTB=8±2, $p<0.05$), suggesting that GM1 also plays a role in both association of Aβ with the membrane and in perforation. **Conclusion** Taken together, our results strongly suggest that membrane lipid composition can affect the ability of Aβ to associate and subsequently perforate the plasma membrane, thereby modulating its toxicity in hippocampal neurons.

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Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Michael J Fox

Alzheimer's Association

Title: Hippocampal volume and dentate gyrus new-born neuron density in a mouse model of apolipoprotein eε4 domain interaction

Authors: *S. O. ADEOSUN[1], X. HOU[2], A. PALMER[2], B. ZHENG[2], R. L. RAFFAI[4], K. H. WEISGRABER[5], J. WANG[2,3];
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Abstract: We previously reported cognitive impairment in young and old mice expressing mouse apoE with domain interaction (Arg-61 mice). Considering the correlation between hippocampal volume and cognitive functions, and apolipoprotein E (apoE) isoform-dependent differences in hippocampal volume in humans, we hypothesized that impaired cognitive function of young Arg-61 mice results from lower hippocampal volume. We measured hippocampal volume and its sub-regions in Nissl stained sections of 5-month old female Arg-61 and C57BL/6J mice and quantified calretinin-positive neurons in the hippocampus by unbiased stereology. We also measured Amyloid beta (Aβ) levels in hippocampal homogenates by dot-blot analysis. Whole hippocampal volume was not different between Arg-61 and C57BL/6J mice; however, the granular cell layer (GCL) volume and the percentage it occupies in the hippocampus were larger in Arg-61 than in C57BL/6J mice. Subgranular zone (SGZ) calretinin (CR)-positive neuron number and density were higher in Arg-61 mice, suggesting that the larger GCL volume may result from more neurons being added to the GCL. Lastly, Aβ -which stimulates ectopic adult neurogenesis in mouse models of Alzheimer disease, was significantly higher in Arg-61 than in C57BL/6J mice. In conclusion, impaired cognitive functions in Arg-61 mice do not result from lower hippocampal volume. In contrast, the larger GCL volume and higher calretinin cell number and density suggest a compensatory attempt which may be due to amyloid beta perturbations, at least in part. Alternatively, these parameters may result from defective neural pruning in Arg-61 mice. Targeting apoEε4 domain interaction may thus be a viable prophylactic/therapeutic approach for apoEε4-dependent pathologies and increased susceptibility of apoEε4 subjects to AD.

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Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

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Topic: C.02. Alzheimer's Disease and Other Dementias

Support: NIH Grant R41-AG048658

Title: Omega-3 fatty acids augment the actions of nuclear receptor agonists in a mouse model of Alzheimer's disease

Authors: *B. CASALI[1], A. W. CORONA[1], M. M. MARIANI[2], C. KARLO[2], K. GHOSAL[4], G. LANDRETH[3];
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Abstract: Alzheimer's disease (AD) is a highly prevalent disorder for which there are no effective therapies. Accumulation of amyloid beta (Aβ) peptides in the brain is associated with impaired cognition and memory, pronounced inflammatory dysregulation, and subsequent amyloid plaque deposition. Thus, drugs which promote the clearance of Aβ peptides and resolution of inflammation may represent viable therapeutic approaches. Agonists of nuclear receptors LXR:RXR and PPAR:RXR act to ameliorate AD-related cognitive impairment and amyloid accumulation in murine models of AD. The use of an agonist to the nuclear receptor RXR, bexarotene, as monotherapy against AD presents potential challenges due to the metabolic perturbations it induces in the periphery, most prominently hypertriglyceridemia. We report that the omega-3 fatty acid docosahexanoic acid (DHA), in combination with bexarotene, enhances LXR:RXR target gene expression of Abca1 and ApoE, reduces soluble forms of Aβ, and abrogates release of pro-inflammatory cytokines and mediators both *in vitro* and in a mouse model of AD. Moreover, DHA abrogates bexarotene-induced hypertriglyceridemia *in vivo*. Importantly, dual therapy promotes reductions in AD pathology and resultant amelioration of cognitive deficits *in vivo*. While monotherapy with either bexarotene or DHA resulted in modest effects *in vitro* and *in vivo*, combined treatment with both agents produced a significant additive benefit on associated AD-related phenotypes, suggesting that targeted combinatorial agents may be beneficial over single agents alone in treating AD.

Disclosures: **B. Casali:** A. Employment/Salary (full or part-time):; Case Western Reserve University. **A.W. Corona:** A. Employment/Salary (full or part-time):; Case Western Reserve University. **M.M. Mariani:** A. Employment/Salary (full or part-time):; Case Western Reserve University. **C. Karlo:** A. Employment/Salary (full or part-time):; Case Western Reserve University. **K. Ghosal:** A. Employment/Salary (full or part-time):; ReXceptor. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Institute for Health. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ReXceptor. Other; ReXceptor. **G. Landreth:** A. Employment/Salary (full or part-time):; Case Western Reserve University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds

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Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

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Support: R01ES024233

R01AG037481

R01AG037919

K01AG044490

Title: High fat diet aggravates memory deficits in APP mice and causes epigenetic changes

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Abstract: Alzheimer’s disease (AD) is a multifactorial disease with various factors that influence risk. Environmental factors such as a diet high in fat and/or cholesterol can affect AD risk by acting on the epigenome. We have previously shown that high fat diet (HFD) exacerbates AD phenotype in APP23 mice and that an LXR agonist ameliorates this effect. 11-month-old APP23 mice were subjected to either control diet or HFD for three months. HFD aggravated spatial learning but not memory retention in a Morris Water Maze (MWM) behavioral paradigm. HFD significantly increased amyloid deposition in hippocampus and cortex as detected by X-34, and 6E10 anti-amyloid beta (Aβ) staining used to characterize compact and diffuse plaques in the brain respectively. To determine the effect of HFD on epigenome we utilized chromatin immunoprecipitation coupled with massive parallel sequencing (ChIP-seq) to map genome-wide changes in several chromatin marks: histone 3 Lys 4 tri-methylation (H3K4me3) and H3K9 acetylation (H4k9ac) associated primarily with active promoters, and H3K27me3 (part of Polycomb repression complex). Functional annotation clustering using DAVID and IPA web

tools revealed that epigenetic changes were mainly clustered in functional categories related to neuronal differentiation, neuron projections and synapses. Additional epigenetic changes were observed associated with mTOR and IGF-1 signaling pathways. These data were further validated in cell culture and *in vivo* using QPCR, Western blotting and IHC. We conclude that HFD causes epigenetic changes that potentially may affect transcriptional activity and expression level of genes important for developing AD, accelerating the course of the disease, or aggravating AD phenotypes.

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Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

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DOD W81XWH-13-1-0384

Title: Bexarotene treatment induced up-regulation of Trem2 and Aβ phagocytosis by microglia in APP/PS1 mice

Authors: *A. MOUNIER[1], K. NAM[2], J. SCHUG[4], N. F. FITZ[2], I. LEFTEROV[3], R. KOLDAMOVA[3];
[1]Envrn. and occupational health, [3]Envrn. and Occup. Hlth., [2]Univ. of Pittsburgh, Pittsburgh, PA; [4]Functional Genomics Core, Dept. of Genetics, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Retinoid X receptors (RXRs) are ligand-activated transcription factors that form permissive heterodimers with Liver X Receptors (LXR). We have previously shown that treatment of APP/PS1 mice with bexarotene, an RXR agonist, induced a significant improvement

of their cognitive performance. Although no effect of bexarotene treatment on plaques load or insoluble Aβ level in the brain was observed, biochemical analysis suggested improved clearance of soluble Aβ, including Aβ oligomers. To investigate the molecular mechanisms underlying this effect, we performed genome-wide differential gene expression analysis using high throughput massively parallel sequencing on libraries generated from cortices of Bexarotene or vehicle treated APP/PS1 mice. We further analyzed the differentially expressed genes using DAVID (Database for Annotation, Visualization and Integrated Discovery) web tool. We determined that the most significant Gene Ontology (GO) Biological Process categories are clustered in GO terms immune response, defense response and immunoglobulin mediated immune response. Chromatin immunoprecipitation (ChIP) with RXR antibody, followed by ChIP-QPCR and RT-QPCR expression assays were used to validate some genes of interest found differentially expressed in response to RXR activation, including the genes coding for the Triggering Receptor Expressed On Myeloid Cells 2 (Trem2), TYRO Protein Tyrosine Kinase Binding Protein (Tyrobp), Complement Component 1 Q Subcomponent (C1q) and Transthyretin (Ttr). Immunofluorescence assays showed significantly increased *in vitro* Aβ phagocytosis by Bexarotene treated BV2 microglial cells. The results of our study demonstrate that in AD model mice expressing human APP, gene networks up-regulated in response to RXR activation by the specific, small molecule, synthetic ligand Bexarotene may influence diverse regulatory pathways that are considered critical for cognitive performance, inflammatory response and Aβ clearance, and may provide an explanation of bexarotene therapeutic effect at the molecular level.

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Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

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Title: Toll-like receptor 4 antagonism leads to protective effects in the E4FAD transgenic mouse model of Alzheimer's disease

Authors: *J. M. YORK[1], L. M. TAI[1], Y.-T. WANG[2], K. P. KOSTER[1], G. R. THATCHER[2], F. NEUMANN[3], M. LADU[1];
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Abstract: Inheritance of the APOE4 gene for apolipoprotein E (apoE) is the primary genetic risk factor for Alzheimer's Disease (AD), yet a lack of understanding of the functional pathways involved in APOE4-associated risk impedes therapeutic design. Neuroinflammation is as an important early contributor to AD pathology and progression, and although the effects of apoE are multifactorial, increasing evidence supports a role for APOE genotype in amyloid-β (Aβ)-induced neuroinflammation in AD. Indeed, our published data in EFAD mice (which overexpress Aβ42 and express human APOE) demonstrate that microgliosis and astrogliosis are greater in E4FAD than E3FAD (expressing APOE4 and APOE3, respectively) mice. In addition, inflammatory mediators, as a result of toll-like receptor 4 (TLR4) activation, are increased in E4FAD mice relative to E3FAD mice. Complementing these *in vivo* findings, our *in vitro* data reveal that stimulation of TLR4 in mixed glial cultures with lipopolysaccharide (LPS; endotoxin) or oligomeric Aβ (oAβ) induces a similar neuroinflammatory response, as characterized by secretion of tumor necrosis factor (TNF)-α, an effect more pronounced with APOE4 than APOE3. Importantly, both LPS- and oAβ-induced responses are inhibited by Rhodobacter sphaeroides (LPS-RS), a biological TLR4 antagonist. In addition, our recent *in vitro* data demonstrate potent TLR4 antagonism of oAβ-induced responses using a novel synthetic glycolipid. Thus, our working hypothesis is that treatment of EFAD mice with small molecules will improve Aβ pathology and cognitive behavior in an isoform-specific manner. Pharmacokinetic (PK) analysis in wild type mice indicates that this novel synthetic compound is brain-penetrant, and approaches the *in vitro* EC50 concentration. Based on these PK and *in vitro* data, treatment of E4FAD mice demonstrate the anti-inflammatory effects of this compound. Together, these findings highlight the important role of APOE4-modulated TLR4 activation by endogenous ligands in AD, and the therapeutic potential of its antagonism.

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Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

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Topic: C.02. Alzheimer's Disease and Other Dementias

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Title: Astrocytic LRP1 mediates brain abeta clearance

Authors: *C.-C. LIU[1], J. HU[1], N. ZHAO[1], J. CIRRITO[2], D. M. HOLTZMAN[2], G. BU[1]; [1]Neurosci. Res. Dept., Mayo Clin., Jacksonville, FL; [2]Washington Univ., St. Louis, MO

Abstract: Alzheimer's disease (AD) has emerged as the most prevalent form of late-life dementia in humans. Accumulation of amyloid-β (Aβ) peptide in the brain is the first critical step in the pathogenesis of AD. While Aβ production is accelerated in familial AD, increasing evidence indicates that impaired clearance of Aβ is more evident in late-onset AD. Aβ accumulation leads to the formation of Aβ aggregates which disturb synaptic functions and may lead to eventual neurodegeneration. Astrocytes, the most abundant cell type in the brain, play an important role in maintaining neuronal homeostasis. The low-density lipoprotein receptor-related protein 1 (LRP1), which is abundantly expressed in neurons and glial cells, has been implicated in the pathogenesis of AD. Here we show that LRP1 plays a critical role in astrocyte-mediated Aβ clearance. Conditional knock-out of the *Lrp1* gene in astrocytes led to increased brain Aβ levels and exacerbated amyloid plaque deposition in amyloid model APP/PS1 mice without affecting Aβ production. Knockdown of LRP1 in primary astrocytes suppressed Aβ uptake and cellular degradation. In addition, silencing of LRP1 in astrocytes resulted in down-regulation of several major Aβ degrading enzymes including matrix metalloproteases MMP-9, neprilysin and insulin-degrading enzyme. Together, our results demonstrate that astrocytic LRP1 plays an important role in the clearance of Aβ. Our findings provide novel mechanistic insights into brain Aβ clearance pathways and have implications on designing new therapeutic strategies to treat AD.

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Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

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Topic: C.02. Alzheimer's Disease and Other Dementias

Title: Investigation of ABCA7 function and potential links to mechanisms underlying Alzheimer's disease

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Abstract: Recent publications from deCODE Genetics and others have identified variants in the lipid transporter, ABCA7 as risk factors for late-onset Alzheimer's Disease (LOAD). In addition, ABCA7 is thought to be involved in pathways increasingly linked to LOAD, including lipid homeostasis and phagocytic clearance of apoptotic cells. As human genetic data for ABCA7 continues to emerge, there is a need for greater understanding of its physiological function and involvement in the disease process. To that end, we describe here a series of biochemical, cell biological and histological studies to investigate the basic biology of ABCA7 and characterize a disease-linked variant. First, we have generated purified ABCA7 using scalable methods and established assays to measure its activity. Second, using ABCA7 reconstituted into proteoliposomes, we have confirmed its substrate-selectivity for phosphatidylserine. Third, we have compared ABCA7 and ABCA1 function in cholesterol efflux from cells and isolated membrane vesicles. Whether ABCA7 transports cholesterol has been controversial, and our data in heterologous cells suggest that ABCA7 does not significantly efflux cholesterol. Fourth, we have examined ABCA7 mRNA and protein localization in native cells and tissues under basal conditions and after various challenges. We have observed that ABCA7 protein clusters in putative phagosomes and endosomes during phagocytosis in rodent microglia, consistent with a role in debris clearance. As part of a comprehensive histological study in multiple tissues, we have also observed ABCA7 protein localization in multiple cell types in the CNS. Finally, we have verified that a recently identified high risk variant is a loss of function. These results contribute to a growing understanding of ABCA7 function in the CNS and potential links to AD.

Disclosures: **P. Denis:** A. Employment/Salary (full or part-time):; Amgen Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Amgen Corporation. **B. Hall:** A. Employment/Salary (full or part-time):; Amgen Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Amgen Corporation. **Y. Wang:** A. Employment/Salary (full or part-time):; Amgen Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Amgen Corporation. **M. Cueva:** A. Employment/Salary (full or part-time):; Amgen Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Amgen Corporation. **J. gray:** A. Employment/Salary (full or part-time):; Amgen

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Employment/Salary (full or part-time):; Amgen Corporation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Amgen Corporation.

Poster

580. Amyloid Precursor Protein: Apolipoprotein E and Cholesterol

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 580.21/C80

Topic: C.02. Alzheimer's Disease and Other Dementias

Support: Zen-11-202716

Title: ABCA1 is necessary for bexarotene-mediated clearance of soluble amyloid beta from the hippocampus of APP/PS1 mice

Authors: *A. W. CORONA, N. KODOMA, B. CASALI, G. E. LANDRETH;
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Abstract: Alzheimer’s disease (AD) is characterized by impaired clearance of amyloid beta (Aβ) peptides leading to neurodegeneration and cognitive impairment. ApoE plays a critical role in the normal proteolytic degradation of soluble Aβ. This effect is dependent upon ABCA1-mediated transfer of phospholipids and cholesterol onto ApoE. To determine if the mechanism of action of the RXR agonist, bexarotene, is dependent on the induction of lipidated-ApoE, we crossed ABCA1-deficient (ABCA1 KO) mice with the APP/PS1 model of AD. Aged ABCA1 WT and ABCA1 KO APP/PS1 mice were treated for 7 days with vehicle or bexarotene (100mg/kg/day). As expected, bexarotene induced ABCA1 and ApoE expression and lipidation in the brain of ABCA1 WT APP/PS1 mice, but not in ABCA1 KO APP/PS1 mice. Bexarotene reduced levels of soluble Aβ 1-40 and 1-42 in the hippocampus of ABCA1 WT APP/PS1 mice, but this effect was absent in ABCA1 KO APP/PS1 mice. In contrast, insoluble levels of Aβ, and plaque loads were unaffected by bexarotene in this study, indicating that ABCA1-mediated ApoE lipidation is more important in clearance of soluble rather than insoluble Aβ. The effect of bexarotene on microglial inflammatory profiles, however, was independent of ABCA1 genotype. Importantly, bexarotene tended to reverse deficits in novel object recognition in ABCA1 WT APP/PS1 mice, but not in ABCA1 KO APP/PS1 mice. These data indicate that ABCA1-induced lipidation of ApoE is necessary for the ability of bexarotene to clear hippocampal soluble Aβ and ameliorate cognitive deficits.

Disclosures: **A.W. Corona:** None. **N. Kodoma:** None. **B. Casali:** None. **G.E. Landreth:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.01/C81

Topic: C.03. Parkinson's Disease

Support: NIH R01 NS052318

NIH R01 NS075012

Title: Longitudinal changes in basal ganglia and cortex using task-based fMRI in early Parkinson's disease

Authors: ***R. G. BURCIU**[1], J. W. CHUNG[1], P. SHUKLA[1], E. OFORI[1], N. R. MCFARLAND[2,3], M. S. OKUN[2,4,3], D. E. VAILLANCOURT[1,2,5];
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Abstract: The pace of functional decline in Parkinson's disease (PD) is not entirely understood. Given that most longitudinal studies of disease progression have examined patients several years apart, there is an increased demand for tracking changes in brain function over a short period of time, within as well as outside the basal ganglia circuit. Here, we evaluated changes over one year in task-based functional magnetic resonance imaging (fMRI) in a large cohort of early stage PD (n = 40) and an age-matched group of healthy individuals (n = 25). A well-established precision grip paradigm was used, where patients were required to produce force with their more affected hand. PD patients were tested following a 14-hour withdrawal from antiparkinsonian medication. Gait, bimanual coordination, and cognitive status were also assessed, at recruitment (baseline) and 1 year later (follow-up). A region of interest (ROI) approach was employed to examine changes in blood-oxygen-level dependent (BOLD) signal in the following cortical and subcortical structures: putamen, hand area of the primary motor cortex (M1), supplementary motor area (SMA), and hand area of the cerebellum (lobules V-VI). Results show no functional change over the course of a year in any of these regions for controls. However, in PD the functional activity of the putamen, hand area in M1, and SMA declined significantly from baseline to follow-up. Other changes in PD included an increase in disease severity based on the

motor section of the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III) and worsening of gait and bimanual coordination. No decline in cognition was detected in PD. In summary, early stages of PD are associated with decreases in the functional activity of key nodes within the basal ganglia and motor cortex but not the cerebellum. Importantly, the decline in cortical regions is steeper than in the basal ganglia, information which may prove crucial in the assessment of novel therapeutic agents in PD.

Disclosures: R.G. Burciu: None. **J.W. Chung:** None. **P. Shukla:** None. **E. Ofori:** None. **N.R. McFarland:** None. **M.S. Okun:** None. **D.E. Vaillancourt:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.02/C82

Topic: C.03. Parkinson’s Disease

Support: John Templeton Foundation Grant #29245

Title: Quantification of striatal dopaminergic uptake in Parkinson’s disease: A new multimodal method combining SPECT DaT and MPRAGE

Authors: *K. SMART, R. DURSO, E. MODESTINO;
Boston Univ. Sch. of Med., Jamaica Plain, MA

Abstract: Parkinson’s disease (PD) is a neurodegenerative disease caused by degeneration of nigral dopaminergic terminals in the caudate and putamen. Currently, when a clinical diagnosis of PD is equivocal, a single-photon emission computed tomography scan using the DaTscan radionuclide (SPECT DaT) is ordered. However, the clinical assessment of SPECT DaT scans depends on radiologists’ subjective judgment, which can pose problems for diagnostic accuracy. Furthermore, research studies generally do not quantify SPECT DaT scans when using them. The aim of this paper is to propose a method of quantification for SPECT DaT scans, to be employed in clinical and research environments. Each of the 4 subjects underwent a SPECT DaT scan and an MPRAGE scan (Magnetization Prepared Rapid Gradient Echo), an anatomical MRI (magnetic resonance image). The SPECT and MPRAGE scans were coregistered, and then a voxel-based quantification of the left and right hemispheric caudate and the putamen was performed in every subject. First, the percentages of voxels with intensities exceeding various pericalcarine baselines were calculated. This baseline was used because the pericalcarine gyrus in the occipital lobe has been shown to have little to no dopaminergic activity on SPECT DaT

scans. Next, asymmetry indices (AI) were calculated for two thresholds whereby the ratio of the voxel percentages in the right to the left hemispheric region was taken. Wilcoxon Signed-Rank tests and bootstrapping analyses were performed on both the caudate and the putamen in all four subjects to determine the significance of any detected asymmetry. The quantification data revealed asymmetries in the voxel intensities between the left and right putamen that were consistent with each subject's side of physical symptom onset: the right-onset PD subjects 1, 2, and 4 had putamen AI values of 11.08, 2.82, and 6.22, respectively, and the left-onset PD subject 3 had a putamen AI value of 0.61. Respectively, subjects 1-4 had caudate AI values of 3.22, 1.46, 1.64, and 2.24. The bootstrapping analyses found these asymmetries to be significant in five of the eight comparisons. In summary, this anatomically accurate, voxel-based quantification has potential to bring greater objectivity to the use of SPECT DaT scans in the diagnosis of PD. This methodology also allows for separately quantifying the caudate and putamen to analyze cognitive symptoms versus motor deficits. The accuracy of the data and the attributed conclusions could be enhanced by the inclusion of partial volume correction (PVC); therefore, future development of this method should involve PVC to account for the intrinsically poor resolution of SPECT scans.

Disclosures: **K. Smart:** None. **R. Durso:** None. **E. Modestino:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.03/C83

Topic: C.03. Parkinson's Disease

Support: Parkinson's Queensland Seeding Grant

Title: Functional neuroimaging of prefrontal cortex in Parkinson's disease using fNIRS: effects of cognitive task during seated and standing postures

Authors: ***G. KERR**, M. MUTHALIB, R. PEGORARO, L. ROEDER, I. STEWART, S. SMITH;
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Abstract: AIM: Cognitive impairment is prevalent in Parkinson's disease (PD). Reduced cognitive function, particularly executive function, has been associated with poorer quality of life, decreased activities of daily living and increased balance and gait disturbance. The concurrent performance of cognitive tasks, while standing or walking also increases postural

instability. Neural circuits involving activation of prefrontal cortex and involved in executive function are thought to be critical for control of balance and gait. This study utilized functional near-infrared spectroscopy (fNIRS) imaging to determine how prefrontal cortex activation is affected during concurrent cognitive and balance tasks. METHODS: We utilized fNIRS to examine pre-frontal cortex alterations in concentration of oxy- (O2Hb) and deoxy-haemoglobin (HHb) in cerebral microcirculation blood vessels during performance of a cognitive task (verbal fluency) involving executive function. During this task participants were either seated or standing quietly on a force plate (Hur Labs, 100Hz). Groups of early stage Parkinson's disease and healthy control participants were assessed according to the following protocol repeated 5 times during sitting and standing: Baseline (30s), Verbal Fluency (30s), Recital of days of the week (30s). RESULTS: Both the control and the PD groups had similar performance in the verbal fluency and the week day recital tasks. In the control group, neuronal activation during the verbal fluency task (relative to baseline) caused an increase in regional blood flow (i.e., neurovascular coupling), which was characterised by an increase in O2Hb and a decrease in HHb in the right dorsolateral prefrontal cortical (DLPFC) region during the seated condition. These changes were observed in the DLPFC bilaterally during the standing condition. For the PD group during the verbal fluency task there was a bilateral increase in DLPFC O2Hb during the seated condition but this was greatly reduced in amplitude. During the standing condition there was negligible change in DLPFC O2Hb in both hemispheres for PD participants. There was negligible change in O2Hb during the week day recital task for both groups. CONCLUSIONS: These changes in O2Hb indicate that PD participants have reduced activation of the DLPFC during the performance of cognitive tasks involving executive function. Furthermore, during standing, activation of the DLPFC is further reduced, in contrast to control participants who have increased bilateral activation. This indicates that people with PD have either reduced activation of the same neural circuits or utilise different neural circuits to complete these tasks.

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Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.04/C84

Topic: C.03. Parkinson's Disease

Support: CIHR

Title: Detecting an olfactory-based biomarker for early stage Parkinson's disease using diffusion tensor imaging

Authors: N. JOSHI[1], T. ROLHEISER[2], J. D. FISK[2], K. P. GOOD[2], N. KHAN[3], G. E. PHILLIPS[2], J. R. MCKELVEY[4], *H. A. ROBERTSON[1];
[1]Dalhousie Univ. Fac Med., Halifax, NS, Canada; [2]Psychiatry, [3]Diagnos. Radiology, [4]Med., Dalhousie Univ., Halifax, NS, Canada

Abstract: Diagnosis of Parkinson's disease (PD) requires the presence of motor symptoms although pre-motor changes such as olfactory loss and the deposition of α-synuclein aggregations in the olfactory bulb and tract precede the emergence of motor symptoms. Biomarkers based on such changes could help identify those at risk of PD. We sought to find biomarkers related to olfactory loss that might differentiate early-stage PD from healthy controls (HC) by using diffusion tensor magnetic resonance imaging (DTI). We used a Region of Interest approach to determine if anterior olfactory structures (AOS: olfactory bulb & tract) exhibit microstructural changes between PD and HC subjects. Ten early-stage (Hoehn and Yahr stage I or II) PD subjects and twenty-six matched HC subjects were compared. Olfaction was tested using the University of Pennsylvania Smell Identification Test (UPSIT). Magnetic resonance imaging employed a 1.5T GE scanner and sequences such as a coronal T2 FRFSE sequence as well as an axial DTI sequence (measuring water diffusion in 55 directions). The AOS on each side of the brain of every subject were traced manually using the coronal T2 images; the tracings were then registered to the DTI images. DTI measures generated included: Fractional Anisotropy (FA), Mean Diffusivity (MD), Axial Diffusivity (AD) and Radial Diffusivity (RD) which were compared between the two groups using a two-way ANOVA with side and disease state as independent variables. UPSIT scores revealed poorer olfaction in PD subjects. DTI-variables including MD, AD and RD were increased bilaterally in AOS of PD patients relative to HC. Additionally, the PD group demonstrated reduced FA in the right AOS relative to HC, and asymmetry of DTI measures of the AOS with reduced FA in right AOS compared to the left; this asymmetry was not seen among HC. Reduced FA in AOS for PD patients has been noted before although asymmetric FA reduction is a novel finding and may represent asymmetric atrophy of AOS white matter in early stage PD. These findings indicate that DTI measures of AOS aside from FA alone can differentiate early stage PD patients from HC and support the use of DTI of AOS in the development of multimodal biomarkers to identify premotor stages of PD.

Disclosures: **N. Joshi:** None. **T. Rolheiser:** None. **J.D. Fisk:** None. **K.P. Good:** None. **N. Khan:** None. **G.E. Phillips:** None. **J.R. McKelvey:** None. **H.A. Robertson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurodyn Inc. F. Consulting Fees (e.g., advisory boards); Neurodyn Inc.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.05/C85

Topic: C.03. Parkinson's Disease

Support: NIH NINDS 5R01NS075321

Title: β-Amyloid PET predicts longitudinal cognitive performance in Parkinson's disease

Authors: *M. C. CAMPBELL[1], E. R. FOSTER[2], J. S. PERLMUTTER[2];
[1]Neurol., Washington Univ. Sch. of Med., Saint Louis, MO; [2]Washington Univ. Sch. of Med., St. Louis, MO

Abstract: Introduction: Several lines of evidence suggest that abnormal β-amyloid (Aβ) deposition occurs in Parkinson disease (PD). Previous research on β-amyloid PET imaging with Pittsburgh compound B (PiB) in PD demonstrates that approximately 15-30% of non-demented PD already have elevated Aβ. However, little is known about the predictive ability of PiB binding for cognitive decline in PD. The purpose of this study was to examine the relationship between baseline PiB binding and longitudinal cognitive changes in PD. Methods: Baseline PiB binding in caudate, brainstem, and averaged across cortical regions (MCBP) and neuropsychological testing were obtained from 70 non-demented PD participants (31 with normal cognition, 39 with cognitive impairment). Follow-up neuropsychological testing was repeated two years after baseline assessment. For each of the primary cognitive domains (attention, memory, visuospatial, language, executive function), composite Z-scores were computed based on the average of the z-transformed individual tests; an overall cognitive composite Z-score was computed as the average of domain Z-scores. Hierarchical linear regressions, controlling for age, education, and baseline cognitive performance, were conducted to test the predictive ability of PiB binding for cognitive performance at the follow-up visit. Results: After controlling for age, education, and baseline cognitive performance, both brainstem and MCPB PiB binding significantly predicted attention performance at the follow-up visit for PD participants (full model, $p < .001$; brainstem R2 change = .03, $p = .03$; MCBP R2 change = .03, $p = .04$). Splitting PD participants by cognitive status revealed that for PD with normal cognition, brainstem PiB binding significantly predicted attention performance (full model, $p < .001$; brainstem R2 change = .14, $p = .009$). For PD with cognitive impairment, baseline brainstem PiB binding predicted memory (full model, $p < .001$; brainstem R2 change = .07, $p = .03$), and visual-spatial performance (full model, $p < .001$; brainstem R2 change = .09, $p = .03$) at follow-up. Conclusion: These data demonstrate that elevated brainstem PiB binding predicts cognitive decline in PD. Most notably, baseline brainstem PiB predicted follow-up cognitive

performance even after controlling for age, education and baseline cognitive performance. These findings suggest that brainstem PiB binding may be a useful prognostic marker of cognitive decline in PD.

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Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.03. Parkinson’s Disease

Support: Michael J. Fox Foundation for Parkinson's Research (MJFF) 320897

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Natural Sciences and Engineering Research Council of Canada (Conseil de Recherches en Sciences Naturelles et en Génie du Canada) 436259-13

Title: Parkinson’s disease targets intrinsic brain networks

Authors: *Y. ZEIGHAMI[1], M. ULLA[2], Y. ITURRIA-MEDINA[1], M. DADAR[1], K. LARCHER[1], V. FONOV[1], A. C. EVANS[1], D. L. COLLINS[1], A. DAGHER[1];
[1]McGIll Univ., Montreal, QC, Canada; [2]Dept. of Neurol., CHU Clermont-Ferrand, Clermont-Ferrand, France

Abstract: Network propagation hypothesis of neurodegenerative diseases (e.g. Alzheimer's disease) proposes that degeneration spreads through brain via intrinsic brain networks. Here we test this hypothesis in Parkinson's disease (PD). We used the following data from the Parkinson's Progression Markers Initiative (PPMI), a multi-center study of de novo PD patients and healthy controls: T1 brain MRI at 3T, the Unified Parkinson’s Disease Rating Scale motor score (UPDRS III) and striatal binding ratio (SBR), a measure of dopamine innervation. Data from 232 PD patients and 117 HC were available. Regional atrophy was calculated using deformation based morphometry (DBM) and decomposed into spatially independent maps using independent

component analysis (ICA). The deformation values from each ICA component were compared between PD and HC. In order to compare PD atrophy to intrinsic brain networks, ICA maps were compared to seed based functional connectivity map with Substantia Nigra (SN) as seed. We also investigated the relation between regional functional connectivity and structural deformation. ICA estimated 30 independent components. PD patients had higher deformation values in only one of the networks (p=0.003 Bonferroni correction). This PD-ICA component includes the entire basal ganglia, amygdala, hippocampus, insula, anterior cingulate cortex, and premotor areas. There was a significant correlation between DBM values in the PD-ICA component and both SBR ($r=0.22$, $p<0.001$) and UPDRS III ($r=-0.26$, $p<0.0001$). The resting state network identified with the SN Seed was spatially correlated only to the PD-ICA network ($r=0.3$), out of the 30 ICA components. Regional functional connectivity was significantly correlated with regional structural deformation ($r = -.41$, $p<.0001$). The set of regions demonstrating disease-related atrophy in PD correspond to an intrinsic network in healthy brain. Moreover, the deformation in a given region was inversely proportional to functional distance from the presumed disease epicenter in the SN. This supports the network propagation hypothesis in PD.

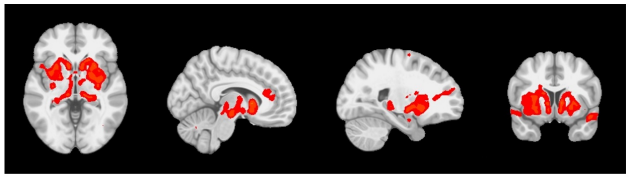

Figure 1. Distribution of Atrophy in Parkinson's Disease, Selected sections in MNI space at coordinates z = -2, x = -8, x = -23, y = 10

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Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.07/C87

Topic: C.03. Parkinson's Disease

Support: The Michael J. Fox Foundation

Title: C-terminal-truncated alpha-synuclein smart molecule: a novel blood-brain barrier permeable diagnostic and therapeutic molecule for Parkinson's disease

Authors: *A. CARTIER, R. BHATT;
ICB International, Inc., La Jolla, CA

Abstract: Development of blood-brain barrier (BBB) permeable biologics that specifically target alpha-synuclein (α-syn) has great clinical potential for treatment, early diagnosis, monitoring of disease progression and therapeutic efficacy of drugs in patients at risk or afflicted with Parkinson's disease (PD). We have developed SMART Molecules (SMs) to deliver diagnostic and therapeutic agents across the BBB to specific targets within the Central Nervous System (CNS). Our SM approach utilizes the target specificity of conventional antibodies, and BBB permeability of small molecule drugs to create novel biologics ideal for *in vivo* imaging of pathological brain lesions and therapeutic purpose. We have generated SMART Molecules for full length (α-syn-SM) and C-terminal truncated alpha-synuclein (CT-α-syn-SM) since α-syn is a major pharmaceutical target for PD as its progressive accumulation, deposition and aggregation is a pathological hallmark of this disorder. Furthermore, CT-α-syn species have been shown to form toxic fragments enhancing α-syn oligomerization. In this study, the unique specificity and BBB permeability of α-syn-SM and CT-α-syn-SM was evaluated. We utilized brain tissues derived from human PD patients and α-syn transgenic (tg) to characterize the specificity of α-syn-SM and CT-α-syn-SM to detect α-syn species. We further assessed the binding specificity of these SMs using peptides corresponding to various regions of full length α-syn. We have also evaluated the BBB permeability of our SMs in α-syn transgenic mice that received a single low dose injection of each SM or a conventional mouse antibody against α-syn. Our data demonstrate that both SMs demonstrate superior blood-brain penetration compared to conventional antibodies, and exquisite specificity for α-syn species. Our long-term objective is to utilize α-syn-SM and CT-α-syn-SM to develop: 1) diagnostic imaging biomarkers in conjunction with an *in vivo* imaging modality, and 2) therapeutic molecules to target and remove toxic forms of α-syn. The clinical utility of these SMs is currently under investigation. This study is partly supported by the Michael J. Fox Foundation.

Disclosures: A. Cartier: None. **R. Bhatt:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.08/C88

Topic: C.03. Parkinson's Disease

Support: NS075321

NS41509

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the American Parkinson Disease Association (APDA) Advanced Research Center of Excellence at Washington University in St Louis

Greater St Louis Chapter of the APDA

Barnes Jewish Hospital Foundation (Elliot Stein Family Fund and Parkinson Disease Research Fund)

Title: Neuroimaging biomarkers for cognitive dysfunction in Parkinson's disease

Authors: *J. S. PERLMUTTER[1], C. BUDDHALA[2], P. T. KOTZBAUER[2], N. J. CAIRNS[3], M. C. CAMPBELL[2];
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Abstract: Neuroimaging with PET biomarkers and resting-state functional connectivity with MRI (rs fcMRI) has provided new insights into the pathophysiology of cognitive dysfunction that occurs in most people with Parkinson disease (PD). We combined these imaging modalities with biochemical and pathologic protein measures from CSF and brain tissue in a large longitudinal cohort of more than 260 people with PD (with or without cognitive impairment) and controls. We have found that comparison of PET data using the Aβ amyloid biomarker [11C]Pittsburgh compound B (PiB) in PD participants with postmortem findings reveals the importance of such assessments for meaningful interpretation of the PET findings, and better understanding of the pathophysiology of dementia associated with PD. Aβ amyloid distribution in PD differs from that in Alzheimer disease, even when controlling for cognitive impairment. Aβ1-42 levels in CSF in those with PD positively correlate with α-synuclein levels suggesting that Aβ amyloid in brain may reflect severity of brain synucleinopathy. Furthermore, reduced coherence of the sensorimotor resting-state functional network correlates with reduced CSF levels of α-synuclein in PD. Functional connectivity within the dorsal attention network (DAN) and default mode network (DMN) decreased over time in non-demented PD participants and baseline resting-state network strength predicted cognitive performance. Together these findings help define the role of proteinopathy in cognitive dysfunction in PD and highlight the importance of multimodal studies to validate neuroimaging biomarkers. Supported by NIH grants NS075321, NS41509, NS058714, and NS48924 from the National Institute of Neurological Disorders and Stroke; the American Parkinson Disease Association (APDA) Advanced Research Center of Excellence at Washington University in St Louis; the Greater St Louis Chapter of the

APDA; and the Barnes Jewish Hospital Foundation (Elliot Stein Family Fund and Parkinson Disease Research Fund).

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Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.09/C89

Topic: C.03. Parkinson’s Disease

Support: NIH T32AG000269-15

Title: Differences in brainstem volumes on MRI in Parkinson's disease patients vs. persons whose DAT scans did not show evidence of dopaminergic deficit (SWEDD)

Authors: *C. D. SCHROEDER, G. T. STEBBINS, J. G. GOLDMAN;
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Abstract: Objective: To compare regional brainstem atrophy patterns on magnetic resonance imaging (MRI) scans in Parkinson’s disease (PD) patients and persons whose DAT scans lack evidence of dopaminergic deficits (SWEDDs). **Background:** Braak’s pathological staging of PD hypothesizes that there are early changes in the brainstem, progressing from the medulla to the midbrain substantia nigra, and eventually the neocortex. Previous studies have shown differences in brainstem volumes between PD patients and healthy controls. SWEDDs have abnormal motor findings (e.g., tremor, dystonia) and thereby be “mistaken” clinically for PD; however, unlike PD patients, they do not exhibit dopaminergic deficits on dopamine transporter (DAT) scans. **Methods:** MRI brain scans (3T Siemens, T1-weighted MPRAGE sequence) and subject characteristics were obtained from the Parkinson's Progression Markers Initiative (PPMI) at 12 month follow-up. The sample included 148 PD patients (clinical symptoms, positive DAT scans) and 23 age-matched SWEDDs (clinical symptoms, negative DAT scans). Whole brain voxel-based morphometry analyses were conducted using SPM8. Images were smoothed with a 6mm kernel. Regions of interest for midbrain, pons, and medulla were identified using the Wake Forest University Pickatlas and extracted from modulated non-linear scans. Gray matter volume differences between PD and SWEDD groups were examined using t-tests. Predictive value of volume for group classification was assessed with a binary logistic regression. **Results:** PD and SWEDD subjects did not differ significantly in age or sex. Compared with the SWEDDs, the PD

group exhibited significant voxel-wise decreased gray matter volume in the midbrain (mean [SD] PD 0.15 [0.02] SWEDDs 0.16 [0.02], p=0.03) and the pons (mean [SD] PD 0.049 [0.007], SWEDDs 0.053 [0.012], p=0.04). In a logistic regression, midbrain volume successfully predicted diagnostic group (χ^2=4.48, p=0.03). **Conclusion:** PD and SWEDD groups could be differentiated by MRI-derived brainstem atrophy patterns, specifically in the midbrain and pons. This finding suggests that midbrain gray matter volume on MRI may be useful in differentiating parkinsonian/movement disorders that may overlap clinically but differ in DAT scan evidence of dopaminergic deficits. **Acknowledgments:** T32AG000269-15 (CDS), Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org.

Disclosures: C.D. Schroeder: A. Employment/Salary (full or part-time):; Rush University Medical Center, Governors State University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH T32AG000269-15. **G.T. Stebbins:** A. Employment/Salary (full or part-time):; Rush University Medical Center. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Institutes of Health, Michael J. Fox Foundation for Parkinson's Research, Dystonia Coalition, CHDI Management, Inc.. F. Consulting Fees (e.g., advisory boards); Adamas Pharmaceuticals, Inc., Ceregene, Inc., CHDI Management, Inc., Ingenix Pharmaceutical Services (i3 Research), Neurocrine Biosciences, Inc.. Other; Other: Editorial Board, Journal of Clinical and Experimental Neuropsychology. **J.G. Goldman:** A. Employment/Salary (full or part-time):; Rush University Medical Center. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH K23NS060949, Michael J. Fox Foundation, Parkinson's Disease Foundation, Rush University, Teva (Moderato study, site-PI). F. Consulting Fees (e.g., advisory boards); Acadia, Pfizer, Teva.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.10/C90

Topic: C.03. Parkinson's Disease

Support: TPP 42-012

Title: Alterations in the default mode network in de novo, untreated Parkinson's disease patients with mild cognitive impairment

Authors: *S. L. KLETZEL[1], B. C. HARTON[1], A. KOPICKI[1,2], A. A. HERROLD[1,3], T. L.-B. PAPE[1,3,4];
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Abstract: In Parkinson's disease (PD), mild cognitive impairment (PD-MCI) is a common non-motor symptom and a risk factor for developing dementia. Currently there are no effective treatment options for PD-MCI. Resting state functional connectivity (rsFC), as measured with Functional Magnetic Resonance Imaging (fMRI), is a method to investigate neurobiological mechanisms underlying cognitive impairment. The Default Mode Network (DMN) is believed to support cognition, and dysfunction of the DMN is associated with cognitive impairment in PD (Baggio, 2015). To date, all reported rsFC PD studies that have investigated cognition have included participants on dopaminergic medication. These medications can influence cortico-striatal network rsFC (Kwak 2010) and it is possible they may influence DMN rsFC. In this study we (i) describe DMN rsFC in newly diagnosed, never medicated PD-MCI patients compared to newly diagnosed, never medicated PD patients with normal cognitive function (PD-NC) and healthy controls (HC) and (ii) correlate cognitive test scores with DMN rsFC between groups. Imaging and neuropsychological data were obtained from the Parkinson's Progression Marker Initiative (PPMI; www.ppmi-info.org). Participants were evaluated for memory, visuospatial function, executive function, and attention. In our data analysis, participants were grouped based on Montreal Cognitive Assessment (MoCA) total scores: PD-NC (MoCA >25; n=25), PD-MCI (MoCA 21-25; n=7) and HC (MoCA >25; n=6). DMN rsFC was assessed using independent component analysis and region of interest analyses. Imaging data revealed that PD-MCI participants had mostly hypoconnectivity in parietal regions, the precuneus and anterior cingulate cortex compared to HC. Verbal fluency scores correlated negatively with connectivity in the right temporal parietal region. Compared to PD-NC, PD-MCI had hyperconnectivity in the ventral prefrontal cortex (PFC) and hypoconnectivity in parietal and frontal cortical regions and the posterior cingulate cortex (PCC). Visuospatial scores correlated negatively with medial PFC and precuneus connectivity. Memory scores correlated positively with left PCC connectivity. These data suggest that there are changes of DMN rsFC in PD-MCI and some of these changes may underlie cognitive impairment. Moreover, such changes cannot be attributed to PD medications. Future analyses will focus on rsFC of other cognitive networks and how these measures correlate with cognitive test performance. Collectively, these imaging and neuropsychological assessments may be useful in identifying PD-MCI biomarkers that can be targeted for cognitive rehabilitation therapies.

Disclosures: **S.L. Kletzel:** None. **B.C. Harton:** None. **A. Kopicki:** None. **A.A. Herrold:** None. **T.L. Pape:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

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Program#/Poster#: 581.11/C91

Topic: C.03. Parkinson's Disease

Support: Biomarkers Across Neurodegenerative Diseases Award - Michael J Fox Foundation

Title: Striatal and thalamic shape alterations in Parkinson's disease

Authors: *A. RAGOTHAMAN[1,2], C. R. K. CHING[2,4], A. MEZHER[2], Z. ABARYAN[2], P. M. THOMPSON[2,3], B. A. GUTMAN[2];
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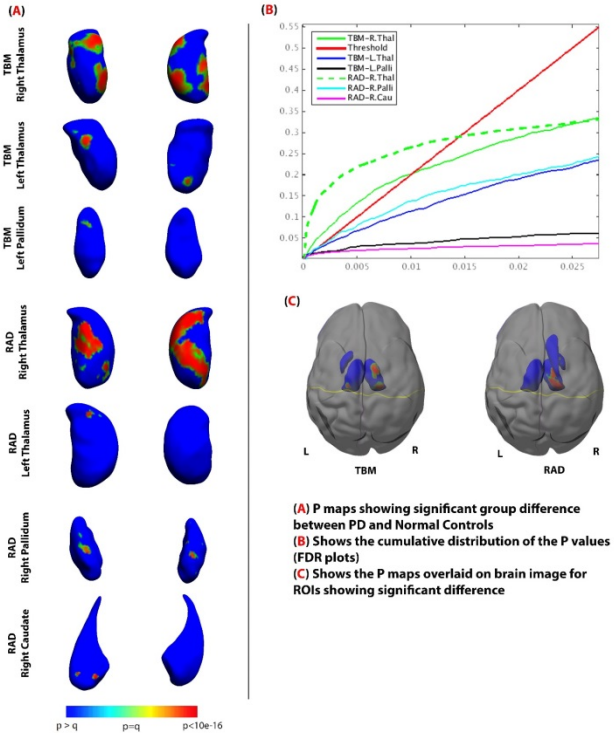
Abstract: Parkinson's disease (PD) is a progressive neurological motor disorder, characterized by difficulty initiating movement, resting tremors, slowness of movement, and muscular stiffness. Standard volumetric analysis of brain images can miss subtle disease related alterations in structures in patients with PD. Shape analysis of subcortical region boundaries reveals more subtle, localized effects. In the present study, we applied, medial demons surface registration, a surface-based parametric shape analysis to seven subcortical regions: left and right amygdala, nucleus accumbens, putamen, caudate, globus pallidus, hippocampus, and thalamus. After shape registration, two surface measures - radial thickness and dilation ratio (Jacobian determinant) - were used to quantify local shape differences. Structural T1-weighted whole-brain MRI scans were obtained from the Parkinson's Progressive Markers Initiative (PPMI; 116M:68F mean age = 61.5M:58.7F healthy controls and 264M:142F mean age = 61.9M:60.9F PD subjects). Subcortical parcellations were obtained using FreeSurfer 5.3. We performed mass-univariate tests for group differences between controls and PD subjects, controlling for age, sex, ICV and handedness. Shape signatures of the following regions were significantly different after False Discovery Rate (FDR) correction for multiple comparisons (critical q in parentheses, higher implies greater effect): right and left thalamus (q=0.0102, q=0.001), left pallidum (q=3.39e-04) for dilation ratio measures (TBM). For radial thickness measures (RAD), significant differences were found in the right and left thalamus (q=0.00144, q=1.69e-04), right pallidum (q=0.0012)

and right caudate (q=4.76e-04). P-maps localizing group differences are shown in Figure 1, and are consistent with previous findings in PPMI. This study suggests that subcortical shape differences can be used as biomarkers for mapping disease effects on the brain.



Disclosures: **A. Ragothaman:** None. **C.R.K. Ching:** None. **A. Mezher:** None. **Z. Abaryan:** None. **P.M. Thompson:** None. **B.A. Gutman:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.12/C92

Topic: C.03. Parkinson’s Disease

Support: NIH

Title: Mild depressive symptoms are related to *in vivo* myelin load in Parkinson’s disease

Authors: ***J. SOJKOVA**[1], D. DEAN, III[1], S. HURLEY[2], S. JOHNSON[1], B. B. BENDLIN[1], A. L. ALEXANDER[1], C. GALLAGHER[1];

[1]Univ. of Wisconsin, Madison, WI; [2]Oxford Ctr. for Functional Magnetic Resonance Imaging of the Brain, Oxford, United Kingdom

Abstract: Title: Mild depressive symptoms are related to *in vivo* myelin load in Parkinson's disease Background: Depression, a common non-motor symptom in Parkinson's disease (PD) affecting approximately 60% of patients, may present as one of the early signs even 5-10 years prior to onset of motor symptoms. Evidence for the role of a myelin-centered model of human brain function in psychiatric conditions has been accumulating with several recent investigations directly focusing on the role of myelin in depression. A novel *in vivo* imaging method, multi-component Driven Equilibrium Single-Pulse Observation of T1 and T2 (mcDESPOT), allows estimation of voxel-wise myelin water fraction (MWF). We hypothesized that greater depressive symptom burden quantified by the Geriatric Dementia rating scale (GDS) will be associated with lower myelin content in PD patients. Methods: 26 nondemented PD patients (mean age: 66.4+/-9.6 years) and 33 controls (mean age: 65.8+/-7.7 years; $p>0.05$) from the Longitudinal MRI Biomarkers in Parkinson's disease study (LMPD) were imaged using mcDESPOT. Depression was assessed using the GDS (30-questions version) during the imaging visit. Given the skewed distribution of GDS scores, log GDS was used as a predictor. Voxel-wise linear regression analysis was used to determine the relationship between depression and myelin content, using Statistical Parametric Mapping software (SPM12). Analyses were adjusted for age, sex and education ($p<0.05$, uncorrected). Results: Patients with PD endorsed more depression compared to controls ($p<0.05$). GDS scores were in the subclinical range, and did not correlate with disease duration or levodopa equivalent dose. In the voxel-wise analysis, higher GDS scores in PD were associated with lower MWF across extensive bilateral subcortical regions, most prominently in posterior brain regions with distinct delineation of posterior forceps of the corpus callosum. Conclusion: To our knowledge, this represents the first investigation of the relationship between myelin load and subclinical depressive symptoms in PD. Using a novel *in vivo* imaging technique, we demonstrate that decrements in myelin load are associated with subclinical levels of depressive symptomatology detected by a psychometric measure. These findings add to a growing body of literature suggesting that depression is associated with myelin alterations. Further investigation is needed to determine the factors that underlie this association.

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Poster

581. Human Imaging Studies in Parkinson's Disease

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Topic: C.03. Parkinson's Disease

Support: NIH 1RC4NS073008-01

NIH P50NS062684

Title: Attention task-related changes to intrinsic functional connectivity in Parkinson's disease

Authors: *T. MADHYASTHA[1], A. LEE[2], M. K. ASKREN[2], J. B. LEVERENZ[3], T. MONTINE[2], T. GRABOWSKI[2];
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Abstract: Correlations among low frequency spontaneous fluctuations in the blood oxygen level-dependent (BOLD) signal at rest reflect the connectivity of intrinsic large-scale networks in the brain. In Parkinson's disease (PD) these networks are disrupted, perhaps contributing to cognitive impairments that ultimately afflict the vast majority of PD patients. To examine the relationship between resting state network disruption and task-related performance, we use a novel technique called network kernel analysis to compare fine-grained network ensembles that include overlapping cortical elements obtained at rest and during the Attention Network Task (ANT) in 24 patients with PD (ages 45-86, 17 male) and 21 controls (ages 41-76, 9 male). PD participants were on average slower and less accurate than controls on the ANT. We confirm that the network kernels obtained during the ANT are the same as those obtained at rest. We compared a general linear model with task-related explanatory variables to one that also incorporated intrinisic network kernel activity to explain cue and target-related activity in regions of interest obtained from Fan et. al, 2005. A likelihood ratio test, Akaike and Bayesian information criteria all indicate that including network kernel activity in a mixed effects model better explains signal in all but two regions of interest. The differences in partial correlations between network kernels in PD and controls were largely the same same during task as at rest (although not necessarily significant after correcting for multiple comparisons), with the exception that at task the correlation between the default mode network and caudate/putamen was lower in PD, and the correlation between the intraparietal sulcus regions and the nucleus accumbens was higher in PD. Despite these group differences, within-subject intrinsic network activity changes in PD reflected task-related normalization (i.e, correlations that were higher in PD than controls at rest decreased during task, and vice versa). We hypothesize that these task-related changes may contribute to task performance. Examining only correlations that were significantly different between PD and controls, we found that greater decrease in correlation between hippocampal activity and the frontal control network during task was related to higher accuracy ($p_{cor} < .001$), and was lower in individual fast trials than slow trials for PD, but not controls. Therefore, intrinsic dynamics may help to understand cognitive impairments in

Parkinson disease by reflecting physiological alterations to networks, compensatory or pathological, that support task performance.

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Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.14/C94

Topic: C.03. Parkinson's Disease

Support: R01NS075012

Title: Striatal - motor cortex functional connectivity in moderate pd and psp

Authors: ***A. S. KURANI**[1], R. G. BURCIU[2], R. SEIDLER[4], M. S. OKUN[3], N. R. MCFARLAND[3], D. E. VAILLANCOURT[2];
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Abstract: Resting state fMRI is used in the current study to measure low frequency fluctuations in the blood oxygen level dependent signal to identify differences in functional connectivity (FC). The study included 20 healthy controls, 20 moderate parkinson disease (PD) and 20 progressive supranuclear palsy (PSP) subjects. All subjects taking medication were tested after overnight withdrawal from medication. Voxel-wise analyses compared each group with controls as well as across patient groups to identify significant clusters ($P < .05$, corrected) of difference. Seed regions included the caudate, anterior/posterior putamen, Pre-SMA and SMA. When patient groups were compared directly, PSP subjects exhibited reduced posterior putamen - temporal lobe and occipital gyrus FC as compared with PD. Z scores in this region were significantly negatively correlated ($R = -0.703$; $p < 0.001$, corrected) with gait measurements and significantly correlated ($R = 0.358$; $p < 0.0491$, FDR corrected) with Purdue Pegboard Test Both task. Also, when comparing PD patients directly with PSP, the SMA seed region showed significantly greater differences in FC patterns across the patient groups compared with the other seed regions. PSP had decreased SMA - cortical motor areas, temporal lobe and posterior cingulate gyrus FC compared with PD. PSP exhibited increased SMA - basal ganglia, inferior parietal lobe and occipital lobe FC compared with PD. Gait severity, as measured by the gait

items of the MDS-UPDRS, was strongly correlated (R=.620; p<0.0002, corrected) with SMA - basal ganglia functional connectivity Z scores in PD and PSP groups. We provide evidence that PSP subjects exhibited greater changes in FC patterns for basal ganglia and cortical motor seed regions when compared with controls and PD subjects. Of the basal ganglia seed ROIs, the posterior putamen showed the largest degree of changes between the patient groups as well as with controls. These findings are supported by previous studies which have found that the posterior putamen is most affected in PD compared with controls, and extends this finding to PSP compared with controls and PD. Our findings suggest also that the posterior putamen is affected to a larger extent in PSP than in PD. Additionally, the SMA seed ROI showed the greatest change in FC across patient groups. The SMA - basal ganglia FC was positively correlated with clinical gait measurements and negatively correlated with manual dexterity measurements. Furthermore, the increased SMA - basal ganglia FC in PSP compared with controls and PD suggests that this pathway is enhanced in PSP and that there may be another pathway mediating the SMA changes observed in PSP.

Disclosures: **A.S. Kurani:** None. **R.G. Burciu:** None. **R. Seidler:** F. Consulting Fees (e.g., advisory boards); University of Florida. **M.S. Okun:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; National Parkinson Foundation, NIH, NPF, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, the Bachmann-Strauss Foundation, and the UF Foundation. **N.R. McFarland:** None. **D.E. Vaillancourt:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH, Bachmann-Strauss Foundation. F. Consulting Fees (e.g., advisory boards); UT Southwestern Medical Center, University of Illinois at Chicago, and Great Lakes NeuroTechnologies.

Poster

581. Human Imaging Studies in Parkinson's Disease

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Topic: C.03. Parkinson’s Disease

Support: BAND-9665 (Alzheimer’s Association and MJFox Foundation)

NIH NS053488

NIH AG043503

Title: Neuroanatomical changes predictive of motor decline in mild Parkinson's disease

Authors: *L. BAEHR, M. GROSSMAN, D. WOLK, C. MCMILLAN;
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Abstract: Parkinson disease (PD) is a progressive neurodegenerative disease that is characterized as a movement disorder. As clinical trials emerge for the treatment of PD it is important to identify early prognostic biomarkers of longitudinal decline. The Unified Parkinson's Disease Rating Scale Part III (UPDRS III) is the most commonly used motor evaluation in the clinical study of PD. In this study we evaluate whether neuroimaging can be used to identify early prognostic estimates of longitudinal UPDRS-III decline in early Parkinson's disease (ePD) patients who are drug naïve and within 2 years of initial diagnosis. We evaluated 83 ePD patients and 70 demographically comparable controls downloaded from the publically available Parkinson's Progression Markers Initiative (PPMI) dataset. All participants had a baseline T1-weighted MRI and UPDRS-III score at baseline and at 24 months. Grey matter density was calculated using Advanced Normalization Tools (ANTs) and we performed voxelwise regression analyses in SPM8 to relate baseline MRI to longitudinal UPDRS-III. The UPDRS-III score was calculated as a total of numeric ratings including measures of rigidity, tremor, gait, and stability for baseline visit and 24-month follow up. PD patients exhibited an average increase in UPDRS-III score of 6.7 points (+/-8.41) across a 24-month period as compared to controls that demonstrated no substantial change from baseline (0.17+/-2.26). A repeated measures ANOVA revealed that diagnosis had a statistically significant effect on UPDRS-III rate of change [$F(1,151)= 39.73$, $p = .001$]. MRI regression analyses related change in UPDRS-III score over a 24-month period to thalamus, putamen, and posterior cingulate ($p<0.05$). Specifically, regions known to support movement regulation, signaling, and intrinsic motor control networks appear to have predictive utility. Our findings are consistent with the hypothesis that neuroimaging may provide a prognostic biomarker of longitudinal motor decline and may be particularly useful in the context of clinical trials for ePD.

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Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.16/C96

Topic: C.03. Parkinson's Disease

Support: Kakenhi 15K19803

Title: Abnormal recruitment of left prefrontal cortex underlies impaired working memory in Parkinson's disease

Authors: ***T. HATTORI**[1,2,4], S. HOROVITZ[2], P. KUNDU[5], R. REYNOLDS[3], C. LUNGU[2], E. WASSERMANN[2], M. HALLETT[2];
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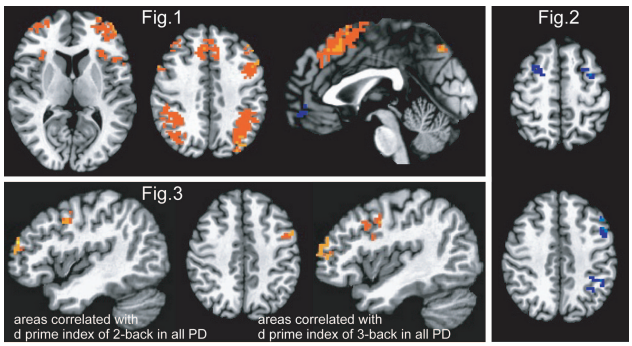
Abstract: Objective: Parkinson's disease (PD) patients often develop cognitive impairment. To date, functional MRI (fMRI) using a cognitive task has been insufficiently investigated during disease evolution. We aimed to identify the neural underpinning of impaired working memory in PD patients. Method: 18 patients with cognitively normal PD (PD-CogNL), 16 with PD with mild cognitive impairment (PD-MCI), and 12 with PD with dementia (PDD) and 18 healthy subjects (controls) were enrolled. While multi-echo time fMRI images were taken in a 3 Tesla MRI scanner, subjects performed an n-back task, including n=0, 1, 2 and 3-back task conditions, and responded each time by pressing a button to indicate whether the current letter was the same as the previous n-back letter. Accuracy for the n-back task was evaluated with the d prime index. Brain activation patterns were compared between patient groups and the control group. The cortical areas where activation was correlated with the d prime index were explored in all PD patient groups. Results: The d prime index for 2- and 3-back tasks was significantly lower in the PD-MCI and PDD groups compared with the controls. In the 1-, 2-, or 3-back task versus 0-back task condition, PD patients and controls had robust activation in the bilateral insular, dorsal cingulate cortex; dorsolateral and ventrolateral prefrontal cortex; and medial and lateral posterior parietal cortex (Fig.1). In the 3-back task versus 0-back task condition, PDD patients had less activation in the frontoparietal network consisting of the prefrontal and parietal cortices, compared with controls (Fig.2). Furthermore, the d prime index for the 2- and 3-back tasks was correlated with activation of the left prefrontal cortex in the 2-back or 3-back versus 0-back task condition in all PD patient groups, respectively (Fig.3). Conclusion: Abnormal recruitment of the frontoparietal network, particularly the left prefrontal cortex, underlies the impaired working memory performance in PD patients.



Disclosures: **T. Hattori:** None. **S. Horovitz:** None. **P. Kundu:** None. **R. Reynolds:** None. **C. Lungu:** None. **E. Wassermann:** None. **M. Hallett:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.17/D1

Topic: C.03. Parkinson's Disease

Support: A121996

Title: Micro-structural differences in white matter between Atypical Parkinsonism and Parkinson's disease

Authors: K. JUNG[1,3], Y. CHANG[3], *M. LEE[1,3], H. S. KIM[1], C. G. CHOI[1], S. C. JUNG[1], C. S. LEE[2], S. J. KIM[1], N. KIM[1,3];
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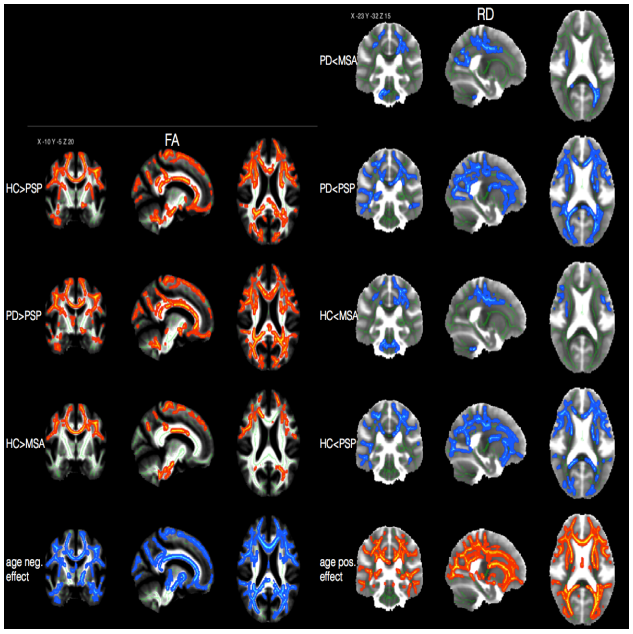
Abstract: Diffusion tensor imaging (DTI) is a useful modality for evaluating micro-structure of white matter of brain. It is well-known for differentiating Parkinsonian syndromes such as multiple system atrophy (MSA) and progressive supra nuclear palsy (PSP). The present study examined differences between MSA, PSP, Parkinson's disease (PD) and normal subjects by using DTI. DTI were obtained from 21 patients with MSA, 24 patients with PSP, 21 patients with PD, and 18 healthy subjects. Fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were computed by using FMRIB's diffusion toolbox. To test differences among them, a tract-based spatial statistics was performed with 1 factor-4 level ANOVA design. The significant level was corrected by controlling the family-wise error rate (alpha value 0.05). All two-sample t-test were considered as two covariates including age and gender. Results of the FA and RD test were significant, but that of MD and AD were not significant. FA of MSA and PSP groups were lower than that of healthy control group and FA of PSP group was lower than that of PD group. RD of MSA and PSP groups were higher than that of PD and healthy control groups. In addition, MD of PSP group was higher than that of PD and healthy control groups. In summary, micro-structure of white matter of MSA and PSP may be different from PD and healthy control. Our results can support that there are different mechanisms among atypical Parkinsonism (MSA and PSP) and PD.



Disclosures: **K. Jung:** None. **Y. Chang:** None. **M. Lee:** None. **H.S. Kim:** None. **C.G. Choi:** None. **S.C. Jung:** None. **C.S. Lee:** None. **S.J. Kim:** None. **N. Kim:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.18/D2

Topic: C.03. Parkinson’s Disease

Title: MAPT gene polymorphism is associated with abnormal uncinate fasciculus integrity in normal population

Authors: *A. BAYANI ERSHADI[1,2], A. ABDOLALIZADEH[3], N. ABBASI[3], B. MOHAJER[3], M. AARABI[3];
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Abstract: Objective: Parkinson’s disease (PD) is a neurodegenerative disorder resulting from the interplay of genetic and environmental factors. One of the disease associated single nucleotide polymorphisms (SNPs) is rs2942168 in the MAPT gene. MAPT polymorphisms are associated with uncinate fasciculus (UF) abnormalities using the Diffusion Tensor Imaging (DTI).

Recently, it has been shown that older adults with rs2942168 may develop mild parkinsonian signs, especially bradykinesia, which has been correlated with Fractional Anisotropy (FA) of UF in PD patients in another study. Thus, we used DTI to investigate white matter integrity of the UF in healthy carriers of this SNP. Methods: Subjects and Genetics: We used Parkinson's Progression Markers Initiative (PPMI; www.ppmi-info.org). Subject's IDs were obtained from the genetic data using PLINK (http://pngu.mgh.harvard.edu/~purcell/plink/) . 11 healthy carriers and 19 age and sex matched healthy controls were included. 3T MRI was used for the diffusion data (64 gradient directions with b-value of 1000 s/mm2). Image Analysis: The DWI data were reconstructed using ExploreDTI. In brief, the diffusion tensors were robustly estimated based on RESTORE algorithm, EPI distortion, head motion correction and the B-matrix reorientation was performed. Deterministic full brain tractography with stopping criteria of FA = 0.2 and 45° curvature threshold was done. Regions of interest (ROI) using "AND" Boolean operator were drawn on the temporal and the ipsilateral frontal in the connecting area of the two lobes. "NOT" was used to omit the anatomically unrelated fibers. Finally, mean FA and mean Apparent Diffusion Coefficient (ADC) of each tract were acquired. Statistics: Statistical Analyses were performed using IBM SPSS v22. Shapiro-Wilk test was used to test for normality. Multivariate analysis of Covariance between FA and ADC was done with age, sex, handedness and education as covariates. Significant results with p-value < 0.05 were reported. Results and Discussion: The normality test of FA and ADC indicated that our data is normally distributed. The results of MANCOVA showed significant differences between Right UF of the carriers and non-carriers ($p = 0.04$, mean estimated: Carriers = 0.435, non-carriers = 0.415). Other results were not significant. We showed that the integrity of right UF is decreased in the carriers of this SNP. Regarding the involvement of UF integrity in bradykinesia, we propose that genetic related impairment in this tract can explain some of the impairments observed in the carriers of the SNP. Further evaluations with clinical data in patients with Parkinson is suggested.

Disclosures: **A. Bayani Ershadi:** None. **A. Abdolalizadeh:** None. **N. Abbasi:** None. **B. Mohajer:** None. **M. Aarabi:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.19/D3

Topic: C.03. Parkinson's Disease

Support: R01 NS 70872 awarded to KHL

The Grainger Foundation.

Title: Intraoperative fmri as a potential biomarker of dbs-evoked adverse effect

Authors: *W. GIBSON[1], P. TESTINI[2], C. EDWARDS[3], J. FELMLEE[4], K. GORNY[4], K. WELKER[4], B. KLASSEN[5], H.-K. MIN[3], K. LEE[2];
[1]Mayo Grad. Sch., Rochester, MN; [2]Neurosurg., [3]Physiol. and Biomed. Engin., [4]Radiology, [5]Neurol., Mayo Clin., Rochester, MN

Abstract: Introduction: Deep brain stimulation (DBS) of the Ventralis Intermedius thalamic nucleus (VIM) is a highly effective therapy for essential tremor (ET). Inappropriate stimulation of the adjacent Ventralis Caudalis nucleus due to targeting error can cause patients to experience unpleasant sensory side effects, which can limit the therapeutic effectiveness of a given DBS electrode. The advent of an intraoperative biomarker of DBS-evoked paresthesias could eliminate the need for patients to remain awake during surgery, which would greatly enhance patient comfort. We aimed to test the hypothesis that intraoperative fMRI in anesthetized patients could be used to detect differential blood oxygen level-dependent (BOLD) effects during DBS at paresthesia-evoking versus non-paresthesia evoking parameters. Methods: Patients with ET underwent bilateral VIM DBS. During battery implantation surgery, a unilateral DBS lead was externalized and connected to an external pulse generator. Stimulation was applied using a block paradigm during gradient echo echo-planar imaging acquisition. While under general anesthesia, patients underwent four fMRI scans, each using a different bipolar stimulation paradigm (0-1+, 1-2+, 2-1+, 3-2+; 3V 130Hz 90us). The presence or absense of stimulation-evoked paresthesia at each setting was evaluated during the first post-operative DBS programming visit. All pulse sequences were previously safety tested, and a strict specific absorption rate limit (< 0.1 W/kg) was observed. All patients provided informed consent and all protocols were approved by Mayo Clinic IRB. Results: Both paresthesia-inducing and non-paresthesia inducing VIM DBS resulted in robust BOLD response in ipsilateral sensorimotor cortex, thalamus, and contralateral cerebellum ($pFWE < 0.05$, one sample t test). Differential activation of these structures was observed due to paresthesia-evoking versus non-paresthesia-evoking parameters ($pFWE < 0.05$, paired t test). Conclusions: Our results suggest that VIM DBS for ET exerts distributed effects on the dentato-rubro-thalamo-cortical network. In addition, we conclude that intraoperative fMRI may hold potential as a biomarker for optimal electrode placement in VIM DBS.

Disclosures: W. Gibson: None. **P. Testini:** None. **C. Edwards:** None. **J. Felmlee:** None. **K. Gorny:** None. **K. Welker:** None. **B. Klassen:** None. **H. Min:** None. **K. Lee:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.20/D4

Topic: C.03. Parkinson's Disease

Title: Diffusion MRI and connectivity of the STN in Parkinson's patients undergoing DBS treatment

Authors: *M. PETERSEN[1], T. E. LUND[4], D. G. ZEIDLER[4], R. SANGIL[4], J. FRANDSEN[4], N. SUNDE[2], F. ROSENDAL[2], K. ØSTERGAARD[3];
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Abstract: High frequency deep brain stimulation (DBS) in the subthalamic nucleus (STN) is an effective treatment for Parkinsonian patients with motor fluctuations and dyskinesia. DBS treatment decreases the use of medication and increases quality of life. In recent years, there has been a tendency to operate on patients at an earlier stage of the disease than before. During DBS surgery, electrodes are positioned bilaterally in the STN and allow stimulation of this region and nearby tissue through electrical impulses. Intraoperative microelectrode recording and test stimulation are imperative in achieving optimal treatment effect and avoiding negative side effects. The surgical planning and target location is traditionally based on direct visual identification of the STN and reference anatomical landmarks on T2- and T1-weighted magnetic resonance imaging (MRI) scans. The STN is known to have three functionally distinct regions (sensorimotor, associative and limbic), as established from primate studies. However, these cannot be identified visually using conventional MRI and the exact DBS target within the STN is based on empirical evidence and surgical experience. The dorsolateral region of the STN receives projections directly from the motor cortex through the 'hyperdirect' cortico-subthalamic pathway. Recent research indicates that this pathway plays a central role in mediating the effects of DBS. Recent advances in diffusion MRI and tractography allow us to map and examine the fiber pathways of the brain non-invasively. By examining the structural connectivity of the STN and nearby regions, we aim to learn more about which pathways are impacted by DBS. Implementing a high-resolution, readout segmented EPI diffusion sequence (1h30min), with reacquisition of segments affected by (cardiac) motion, combined with an advanced probabilistic tractography method (based on constrained spherical deconvolution), we have demonstrated an STN connectivity pattern highly consistent with the known anatomy of the region. We have furthermore been able to delineate a structural pathway consistent with the hyperdirect pathway, projecting to a part of the dorsolateral STN. We are currently refining and evaluating this technique as part of the pre-surgical planning for DBS treatment. Identification of the hyperdirect pathway and sensorimotor region of the STN would be an important contribution to this planning

phase. Once established and standardized, this technique could prove invaluable for optimizing neurosurgical planning by allowing us to target specific fiber pathways.

Disclosures: **M. Petersen:** None. **T.E. Lund:** None. **D.G. Zeidler:** None. **R. Sangil:** None. **J. Frandsen:** None. **N. Sunde:** None. **F. Rosendal:** None. **K. Østergaard:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.21/D5

Topic: C.03. Parkinson's Disease

Support: Scientific Research (B) No. 16390348 from Japan Society for the Promotion of Science

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Scientific Research (C) No. 20591033 from Japan Society for the Promotion of Science

Scientific Research (C) No. 23591287 from Japan Society for the Promotion of Science

Title: Striatal density of adenosine A1 receptors in early Parkinson's disease measured with [C-11]MPDX PET

Authors: *M. MISHINA[1,3], M. SUZUKI[4,3], K. ISHII[3], Y. KIMURA[3,5], K. ISHIBASHI[3], M. SAKATA[3], K. ODA[3,6], J. TOYOHARA[3], S. KOBAYASHI[7], H. NAGAYAMA[2], S. KITAMURA[8], K. KIMURA[2], K. ISHIWATA[3];
[1]Dept. of Neuro-pathophysiological imaging, Grad. Sch. of Med., [2]Dept. of Neurolog. Science, Grad. Sch. of Med., Nippon Med. Sch., Tokyo, Japan; [3]Diagnos. Neuroimaging Res., Tokyo Metropolitan Inst. of Gerontology, Tokyo, Japan; [4]Dept. of Neurol., Katsushika Med. Center, The Jikei Univ. Sch. of Med., Tokyo, Japan; [5]Dept. of Computat. Systems Biology, Fac. of Biology-Oriented Sci. & Technol., Kinki Univ., Wakayama, Japan; [6]Dept. of Radiological Technology, Fac. of Hlth. Sci., Hokkaido Univ. of Sci., Hokkaido, Japan; [7]Dept. of Neurosurg., Nippon Med. Sch. Chiba Hokusoh Hosp., Chiba, Japan; [8]Med. Ctr. for Dementia, Nippon Med. Sch. Musashi Kosugi Hosp., Kanagawa, Japan

Abstract: Objective: Adenosine A_1 receptors (A_1Rs) interact negatively with dopamine D_1 receptors (D_1Rs) in direct pathway neurons of basal ganglia circuits, while adenosine A_{2A} receptors (A_{2A}Rs) negatively interact with dopamine D_2 receptors (D_2Rs) in indirect pathway neurons. We recently reported that A_{2A}Rs were asymmetrically down-regulated in de-novo patients with Parkinson's disease (PD), and were increased in the putamen of PD patients with dyskinesia (1). However, the roles of A_1Rs remain unclear in the PD patients unlike A_{2A}Rs. In this study, we investigated striatal density for A_1Rs in de-novo PD patients, measured with positron emission tomography (PET) and [7-methyl-^{11}C]-(*E*)-8-(3,4,5-trimethoxystyryl)-1,3,7-trimethylxanthine (^{11}C-MPDX). **Methods:** We studied 10 de-novo PD patients. To confirm early diagnosis of PD, they were also examined for dopamine transporters (DATs) and D_2Rs by PET using ^{11}C-2β-carbomethoxy-3β-(4-fluorophenyl) tropane (^{11}C-CFT) and ^{11}C-raclopride (^{11}C-RAC), respectively. We also recruited 10 elderly healthy volunteers for ^{11}C-MPDX PET and 8 volunteers for ^{11}C-CFT and ^{11}C-RAC PET. A dynamic series of decay-corrected PET scans was performed for 60 minutes starting at the time of the injection of 700 MBq of ^{11}C-MPDX. The values for binding potential (BP_{ND}) in the putamen and head of caudate nucleus were calculated using an averaged tissue time activity curve (tTAC) and the Logan graphical analysis assuming that the k_2 in the cerebellum as a reference region was 0.23 l/min (2). For DATs and D_2Rs, we also calculated the uptake ratio index (*URI* = {uptake in putamen - uptake in cerebellum}/{uptake in cerebellum}) of ^{11}C-CFT PET and ^{11}C-RAC PET. Unpaired *t*-test was used to compare the BP_{ND} of ^{11}C-MPDX and *URI* of ^{11}C-CFT and ^{11}C-RAC PET. The level of significance was set at $p<0.05$. **Results**: There was no significant difference with the BP_{ND} for ^{11}C-MPDX between the patients and the controls, although PET demonstrated decrease of the *URI* of ^{11}C-CFT and increase of the *URI* of ^{11}C-RAC in the patients. In the patient with PD, we observed putaminal asymmetry in the *URIs* of ^{11}C-CFT and ^{11}C-RAC but not the BP_{ND} for [^{11}C]MPDX. **Conclusion**: In the putamen of early PD, D_2Rs are asymmetrically up-regulated and A_{2A}Rs are asymmetrically down-regulated as compensation for the decrease of dopamine (1). However, past studies did not demonstrate such alteration in D_1Rs of PD measured with [^{11}C]SCH23390 PET. Our study also suggested that A_1Rs seemed to be monotonous as well as D_1Rs in the striatum, and that the direct pathway was not involved in early PD. **References**: 1. Mishina M, et al., PLoS One 6: e17338, 2011 2. Kimura Y, et al., Nucl Med Biol 31:975-981, 2004

Disclosures: M. Mishina: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; apan Society for the Promotion of Science. **M. Suzuki:** None. **K. Ishii:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Japan Society for the Promotion of Science. **Y. Kimura:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship

even if those funds come to an institution.; Japan Society for the Promotion of Science. **K. Ishibashi:** None. **M. Sakata:** None. **K. Oda:** None. **J. Toyohara:** None. **S. Kobayashi:** None. **H. Nagayama:** None. **S. Kitamura:** None. **K. Kimura:** None. **K. Ishiwata:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Japan Society for the Promotion of Science.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.22/D6

Topic: C.03. Parkinson's Disease

Support: German Research Foundation (KFO 219, TP10)

Title: Overlapping neural correlates of impulsivity and hypomania in Parkinson's disease

Authors: *F. SCHWARTZ[1], M. TAHMASIAN[1,2], K. WILLIAMSON[1], L. ROCHHAUSEN[1], F. MAIER[1], L. TIMMERMANN[1], A. DRZEZGA[2], T. VAN EIMEREN[2], C. EGGERS[1]; [1]Neurol., Univ. Hosp. of Cologne, Koeln, Germany; [2]Nuclear medicine, Univsersity Hosp. of Cologne, Koeln, Germany

Abstract: Impulsive behaviors and hypomania are common non-motor symptoms in Parkinson's disease (PD). Several neuroimaging studies demonstrated particular brain regions being involved in impulsive behavior including the orbitofrontal cortex, anterior cingulate cortex, medial prefrontal cortex and insula. Moreover, other studies revealed brain regions including the anterior cingulate and parahippocampal cortex, as well as inferior frontal gyrus being associated with hypomania. The aim of this study is to find out the regional similarities associated with impulsivity or hypomania in PD. We recruited 24 right-handed, non-demented, not-depressed PD patients and performed two separate multiple regression analyses between FDG-metabolism data and total Barratt Impulsiveness Scale (BIS 11) scores and between FDG-metabolism data and Mania Self-Rating Scale (MSS) scores in SPM8. Subsequently, we compared FDG-metabolism associated with impulsivity and hypomania. Data demonstrated overlapping regions in the middle frontal gyrus, superior frontal gyrus, and supplementary motor area. Our findings provide evidence that impulsivity and hypomania in PD have overlapping neural correlates, suggesting specific brain areas being linked with both of the symptoms.

Disclosures: **F. Schwartz:** A. Employment/Salary (full or part-time):; German Research Foundation (KFO 219, TP 10). **M. Tahmasian:** None. **K. Williamson:** None. **L. Rochhausen:** None. **F. Maier:** None. **L. Timmermann:** None. **A. Drzezga:** None. **T. van Eimeren:** None. **C. Eggers:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.23/D7

Topic: C.03. Parkinson's Disease

Support: German Research Foundation (KFO 219, TP10)

Title: Impulsivity is associated with increased metabolism of the fronto-insular network in Parkinson's disease

Authors: ***M. TAHMASIAN**[1,2], L. ROCHHAUSEN[1], F. MAIER[1], K. L. WILLIAMSON[1], A. DRZEZGA[2], L. TIMMERMANN[1], T. VAN EIMEREN[2,1], C. EGGERS[1];
[1]Dept. of Neurol., [2]Dept. of Nuclear medicine, Univ. Hosp. of Cologne, Koeln, Germany

Abstract: Neuroimaging studies demonstrated that the fronto-insular network is involved in impulsive behaviors. We aimed to compare glucose metabolism (as proxy of neural activity) among patients with Parkinson's disease (PD), who presented different levels of impulsivity. Twenty-four PD patients were divided into two groups based on their Barratt Impulsiveness Scale 11 (BIS) scores. Subjects underwent 18-Fluorodeoxyglucose positron emission tomography (FDG-PET) and voxel-wise group difference of FDG-metabolism was analyzed in SPM8. Subsequently, we performed partial correlation analysis between the FDG-metabolism and BIS scores, controlling for covariates of no-interest (i.e. age, sex, severity of disease and levodopa equivalent daily doses). Voxel-wise group comparison revealed higher FDG-metabolism in the right orbitofrontal cortex, anterior cingulate cortex, medial prefrontal cortex, and insula in patients with higher impulsivity compared to patients with lower impulsivity. Moreover, patients showed a positive correlation between the FDG-metabolism and BIS scores. Our findings provide evidence that higher impulsivity is associated with increased FDG-metabolism within the fronto-insular network in PD.

Disclosures: **M. Tahmasian:** None. **L. Rochhausen:** None. **F. Maier:** None. **K.L. Williamson:** None. **A. Drzezga:** None. **L. Timmermann:** None. **T. van Eimeren:** None. **C. Eggers:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.24/D8

Topic: C.03. Parkinson's Disease

Support: Grant ID 6361.03

Title: Studies towards the development of a PET tracer for aggregated α-synuclein

Authors: G. MCALLISTER[1], D. HARDICK[1], D. MITCHELL[1], K. NASH[1], J. EBERLING[2], R. MACH[3], P. KOTZBAUER[4], Z. TU[4], E. BORRONI[5], M. HONER[5], L. GOBBI[5], S. MASON[6], W. KLUNK[6], *C. A. MATHIS[7];
[1]BioFocus, a Charles River Co., Saffron Walden, United Kingdom; [2]Michael J. Fox Fndn., New York, NY; [3]Univ. of Pennsylvania, Philadelphia, PA; [4]Washington Univ., St Louis, MO; [5]Roche, Basel, Switzerland; [6]Univ. of Pittsburgh, Pittsburgh, PA; [7]B-938 PUH, Pittsburgh, PA

Abstract: Accumulation of aggregated α-synuclein in Lewy bodies and Lewy neurites is the pathological hallmark of Parkinson's disease (PD). Accumulation of aggregated α-synuclein in dopaminergic neurons accompanies neuronal degeneration leading to motor symptoms associated with the disease. To date, there is no agent available to image aggregated α-synuclein *in vivo*, which would benefit disease diagnosis and monitoring, patient selection for clinical trial and monitoring efficacy of a potential therapeutic. In this poster, we will describe research funded by the Michael J Fox Foundation (MJFF) towards the development of an imaging agent capable of selectively detecting aggregated α-synuclein in human patients. The development of a radiolabelled screening ligand to enable screening of compounds in PD brain tissue will be presented along with the approach being used to optimise ligands. Compound properties have been optimised relative to successful clinical imaging agents and successful brain uptake will be presented for an example containing a positron emitting isotope. Data showing how radiolabelled compounds detect aggregated human α-synuclein in a transgenic mouse brain model (A30P) will be included.

Disclosures: **G. McAllister:** A. Employment/Salary (full or part-time):; BioFocus. **D. Hardick:** A. Employment/Salary (full or part-time):; BioFocus. **D. Mitchell:** A. Employment/Salary (full or part-time):; BioFocus. **K. Nash:** A. Employment/Salary (full or part-time):; BioFocus. **J. Eberling:** None. **R. Mach:** None. **P. Kotzbauer:** None. **Z. Tu:** None. **E. Borroni:** None. **M. Honer:** None. **L. Gobbi:** None. **S. Mason:** None. **W. Klunk:** None. **C.A. Mathis:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.25/D9

Topic: C.03. Parkinson's Disease

Support: NIH Grant MH092797

NIH Grant NS075527

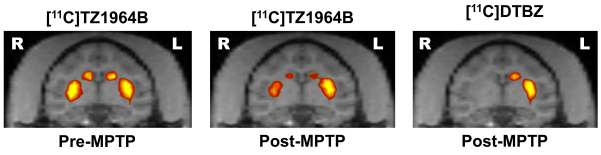
NIH Grant NS061025

Title: *In vitro* characterization of a C-11 or H-3 labeled PDE10A radioligand and its potential implementation for progression of Parkinson's disease

Authors: H. LIU, H. JIN, X. YUE, X. ZHANG, J. LI, H. FLORES, Y. SU, J. S. PERLMUTTER, *Z. TU;
Washington Univ., Saint Louis, MO

Abstract: PET imaging has provided a great tool for *in vivo* measurement of impaired striatal dopaminergic function in Parkinson disease (PD). However, the striatal uptake of current presynaptic dopaminergic ligands in the advanced stage of PD shows a flooring effect and is not correlated well with the full severity of motor parkinsonism. Phosphodiesterase 10A (PDE10A), a postsynaptic biomarker, plays a key role in the regulation of brain striatal signaling. PET imaging with a PDE10A radioligand may serve as an alternative measurement of striatal signaling dysfunction in PD. Here, we further characterized the *in vitro* binding properties of a C-11 or H-3 labeled PDE10A radioligand [^{11}C]**TZ1964B or** [^{3}H]**TZ1964B**, and evaluated its potential as a biomarker for PD progression using MPTP nonhuman primate (NHP) model of PD. *In vitro* binding assays in rat striatum homogenates and *in vitro* autoradiographic studies in rat brain slices revealed a nanomolar binding affinity of the tritiated analog [^{3}H]**TZ1964B** to rat striatum (K_d =1.25 ± 0.20 nM). The striatal binding of [^{3}H]**TZ1964B** was blocked by a PDE10A inhibitor MP-10. Both autoradiography and microPET imaging confirmed that the specific binding of the radioligand was found in the striatum (target region) but not in the cerebellum (reference region), with a target-to-reference ratio of 5.50-7.50. In the MPTP-treated NHP, the striatal binding potential (BP_{ND}) of [^{11}C]**TZ1964B** in the infused (right) side was 40-60% lower compared to the contralateral (left) side, while the tracer uptake of [^{11}C]**DTBZ**, a well-known vesicular monoamine transporter 2 radioligand, is invisible, only 5-10% remaining in the lesioned striatum. The data demonstrated [^{3}H]**TZ1964B** has a high binding affinity and good specificity for PDE10A. Moreover, [^{11}C]**TZ1964B** is able to assess the decline of the striatal

PDE10A expression in NHPs following MPTP treatment, suggesting PET measurement of the decrease of PDE10A in striatum may be a more accurate methodology for monitoring progression of PD, especially in the advanced stage.



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Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.26/D10

Topic: C.03. Parkinson’s Disease

Support: Charles Dana Foundation

Pennsylvania Tobacco Settlement Biomedical Research Fund

Penn State University Brain Research Funds

Title: Early onset Parkinson's disease (EOPD) progression as monitored by hyperechogenicity of the substantia nigra (SN)

Authors: ***S. RAVI**[1], K. VENKITESWARAN[1], V. SHIVKUMAR[1], N. HARID[1], T. GILMOUR[1], C. LIEU[1], R. SAADI[1], D. DANG[1], J.-L. WANG[2], Q. YANG[2], T. SUBRAMANIAN[1];
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Abstract: Early Onset Parkinson’s Disease (EOPD) is characterized by disease onset between ages 41-60, have high risk for treatment related complications, and need close monitoring for disease progression. Substantia nigra (SN) hyperechogenicity measured by Transcranial Sonography (TCS) is an established biomarker to differentiate PD from other forms of parkinsonism. We tested the hypothesis that SN hyperechogenicity can be used as a biomarker for disease progression from stage I (unilateral parkinsonism) to stage II (bilateral parkinsonism)

in EOPD patients. A total of 27 EOPD patients who met UK Brain Bank criteria for PD, did not have genetic forms of PD, and were in Stage I disease as determined by the Unified Parkinson's Disease Rating Scale (UPDRS) in the "off" state were offered this prospective single blind study. TCS was performed and evaluated by a blinded rater using a Siemens Acuson Sequoia Ultrasound system (2.5 MHz transducer). Planimetric measurements of SN hyperechogenicity >0.2 cm^2 were classified as significant on each side. Three patients had poor acoustic window, 1 patient dropped out, and 23 patients completed the study. Patients were seen for baseline evaluations (V1), returned for visit 2 (V2) 1 year later and then for visit 3 (V3) 1.5 years post V1, and visit 4 (V4) 2 years post V1. At V1, hyperechogenicity that met >0.2cm^2 area by planimetry was only found on the contralateral SN (N=22) in all but one patient. Side specific UPDRS on the unaffected side was 0 in all enrolled subjects at V1, including the one patient with bilateral SN hyperechogenicity >0.2cm^2. At V1 mean contralateral and ipsilateral SN hyperechogenicity was 0.267 ± 0.046 cm^2 and 0.091 ± 0.079 cm^2 respectively. By V2, 48% of the patients displayed hyperechogenicity above the 0.2cm^2 threshold ipsilaterally. By V4, the mean ipsilateral SN hyperechogenicity was measured to be 0.294 ± 0.062 cm^2. Mean UPDRS score was 12.04 ± 1.022 at V1 and 17.92± 2.142 at V4. Twenty-two percent of the subjects showed an average SN hyperechogenicity progression time to reach threshold ipsilaterally of 603 ± 50 days. Forty-eight percent of the subjects showed an average progression time of 401 ± 100 days. Patients with right-side symptom onset showed an ipsilateral progression rate of 0.000225 ± 7.68E-05 cm^2/day. Patients with left-side symptom onset showed an ipsilateral progression rate of 0.000247 ± 6.04E-05 cm^2/day. In all 22 patients ipsilateral SN hyperechogenicity gradually increased in area to exceed the 0.2 cm^2 threshold prior to developing stage II disease as determined by the UPDRS part III testing, indicating its usefulness as a biomarker for EOPD progression from stage I to stage II.

Disclosures: **S. Ravi:** None. **K. Venkiteswaran:** None. **V. Shivkumar:** None. **N. Harid:** None. **T. Gilmour:** None. **C. Lieu:** None. **R. Saadi:** None. **D. Dang:** None. **J. Wang:** None. **Q. Yang:** None. **T. Subramanian:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 581.27/D11

Topic: C.03. Parkinson's Disease

Title: DNMT3B polymorphisms is associated with Parkinson's disease

Authors: *J. PEZZI[1], C. M. B. ENS[1], M. FIEGENBAUM[1], A. F. SCHUMACHER-SCHUH[2], M. L. F. CHAVES[2], A. L. CAMOZZATO[1];
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Abstract: Background: Parkinson's disease (PD) is a neurodegenerative disorder mainly characterized by motor symptoms, such as bradykinesia, rigidity and rest tremor. Epigenetic mechanisms have been implicated in syndromes associated with neurodegenerative disorder, but little is known about the role of epigenetics in PD. DNA methylation, one of the main epigenetic mechanisms, is a complex process carried out by specific enzymes, such as DNMT1 and DNMT3B. This study aimed to investigate the association between DNMT1 and DNMT3B polymorphisms and PD. Methods: Three hundred and twenty-eight subjects [108 healthy controls (HC) and 220 with PD] were assessed. DNA was obtained from whole blood, and genotypes were detected by an allelic discrimination assay using TaqMan® MGB probes on a real-time PCR system. The polymorphisms studied were rs2162560 and rs759920 (DNMT1) and rs998382, rs2424913 and rs2424932 (DNMT3B). Results: For both genes, the polymorphisms were in strong linkage disequilibrium. For two of the polymorphisms investigated, considering the DNMT3B enzyme, the minor allele was associated with Parkinson's disease (rs998382: 31.07% HC vs. 51% PD, OR 2.01, $p<0.001$; rs2424913: 35.04% vs. 50%, OR 1.96, $p<0.046$). No significant difference between PD and the control group were observed for DNMT1 polymorphisms. Conclusions: This study is one of the first describing a significant association between DNMT3B polymorphisms and PD. This enzyme, which is responsible for methylation in a general way, may be involved in PD.

Disclosures: J. Pezzi: None. **C.M.B. Ens:** None. **M. Fiegenbaum:** None. **A.F. Schumacher-Schuh:** None. **M.L.F. Chaves:** None. **A.L. Camozzato:** None.

Poster

581. Human Imaging Studies in Parkinson's Disease

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Program#/Poster#: 581.28/D12

Topic: C.03. Parkinson’s Disease

Support: 7th EU programme V-TIME GA 278169

Title: Cholinergic system and mobility: a TMS study to unveil the effect of motor-cognitive combined rehabilitation in Parkinson’s disease

Authors: *L. AVANZINO[1], E. PELOSIN[1], C. OGLIASTRO[1], G. LAGRAVINESE[1], A. RAVASCHIO[1], A. MIRELMAN[2], J. M. HAUSDORFF[2], G. ABBRUZZESE[1];
[1]Univ. of Genoa, Genoa, Italy; [2]Tel-Aviv Med. Ctr., Tel-Aviv, Israel

Abstract: Patients with Parkinson's disease (PD) have a heightened risk of falls and a reduced ability to allocate attention. Deficits in the cholinergic system may contribute to both of these problems. Based on the assumptions that brain plasticity requires both physical and behavioural interventions that are tailored to reorganize specific brain circuits, it has been shown that exercise could enhance neuroplasticity targeting motor and cognitive circuitry. The aim of the present study was to assess the effects of a motor-cognitive combined rehabilitative approach on cholinergic function in patients affected by PD. This study involved 11 PD patients (mean age: 74 ±6) with a history of 2 or more falls recruited for the V-TIME study[1]. Cholinergic activity in the brain was estimated with short latency afferent inhibition (SAI), a TMS technique that assesses an inhibitory circuit in the sensorimotor cortex. SAI was measured by conditioning motor evoked potentials, elicited by TMS of the motor cortex, with electrical stimuli delivered to the median nerve at different inter-stimulus intervals (ISI) ranging around 20 ms. Motor-cognitive combined rehabilitation consisted of a multi-modal treadmill-training program augmented by virtual reality[1]. Participants were trained for 12 weeks, 3 times a week. TMS evaluations were performed at baseline (V1), after 6 weeks of treatment (V2), at the end of the 12 weeks training program (V3) and 1 month after the end of the treatment (V4). At baseline, data collected from the PD population were compared to those collected in 15 age- matched healthy subjects by means of a RM-ANOVA with GROUP and ISI as main factors. The effect of training on SAI in PD was evaluated by means of a RM ANOVA with VISIT and ISI as main factors. Results showed that, at V1, SAI was decreased in PD with respect to healthy subjects ($p<0.05$). The comparison of different doses of training on cortical cholinergic activity showed a significant effect of VISIT ($p=0.042$). SAI was increased already after 6 weeks of treatment and remained increased after 12 weeks training and 1 month after the end of training, with respect to baseline ($p <0.05$). In conclusion, our data showed that PD patients had a weakened SAI, a neurophysiological measure of central cholinergic transmission. Further, a motor-cognitive combined rehabilitation induced measurable changes of short latency afferent inhibition, thus suggesting plastic modifications of cholinergic transmission. References [1]Mirelman A et al. V-TIME: a treadmill training program augmented by virtual reality to decrease fall risk in older adults: study design of a randomized controlled trial. BMC Neurol. 2013

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Poster

582. Therapeutics of Parkinson's Disease: Clinical Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 582.01/D13

Topic: C.03. Parkinson's Disease

Support: Dept. of Anethesiology, UW SMPH

International Anesthesia Research Society

Title: Dexmedetoidine modulates neuronal activity in subthalamic nucleus during surgery for Parkinson's disease

Authors: A. RAZ[1], C. A. AMLONG[1], *M. I. BANKS[2], D. A. RUSY[1], K. A. SILLAY[1,3]; [1]Anesthesiol., [2]Dept. of Anesthesiol., Univ. of Wisconsin, Madison, WI; [3]Semmes-Murphey Neurologic & Spine Inst., Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: Introduction: Implantation of chronic electrodes for deep brain stimulation (DBS) in the sub-thalamic nucleus (STN) is often performed using micro-electrode recordings (MER). When possible, this is performed purely under local anesthesia to avoid interference of the anesthetic drugs with the MER. However, the absence of sedation may lead to discomfort and anxiety for the patient, which can limit the procedure and occasionally even expose the patient to risk. Previous studies have demonstrated that dexmedetomidine is a useful sedative for these procedures. However, there is limited information regarding its effect on neural activity in the STN and hence its effect on MER quality. We recorded the activity of STN neurons in Parkinson's patients undergoing DBS electrode implantation with dexmedetomidine sedation to evaluate its effect. **Methods:** Following IRB approval, and patient consent, we recorded the activity of electrode trajectories in five patients undergoing bilateral DBS electrode implantation in the STN for the treatment of advanced Parkinson's disease. Following STN identification on the second side electrode advancement was paused. Neuronal activity was recorded at this point while patients were sedated with dexmedetomidine and then allowed to wake up. We compared the root mean square (RMS) and beta band (13-30Hz) oscillation power of the multi-unit electrical activity recorded by the microelectrode before, during and after recovery from sedation. RMS was normalized to values recorded in the white matter. **Results:** We were able to achieve a satisfactory level of sedation (observer's assessment of alertness/sedation of 1-3) with dexmedetomidine during the allocated time in 4/5 patients. MUA during dexmedetomidine sedation was decreased in all patients. Mean normalized RMS dropped from 2.8±1.5 to 1.6±1.1 during sedation (0=0.026 paired ttest). Total power in the beta band did not significantly change (p=0.34 paired ttest). Recovery from dexmedetomidine was slow, and in all patients the normalized RMS values did not reach baseline levels during the time allocated for the study (30 minutes). **Conclusions:** In this small sample, we demonstrated that dexmedetomidine decreased

average neuronal firing in the STN, as expressed in the RMS of the multi-unit activity. As multiunit activity is the major factor in determining the STN borders during MER, it would be prudent to avoid using this drug during this procedure. The slow recovery from this effect does not support the use of dexmedetomidine even during early phases of the procedure.

Disclosures: **A. Raz:** None. **C.A. Amlong:** None. **M.I. Banks:** None. **D.A. Rusy:** None. **K.A. Sillay:** None.

Poster

582. Therapeutics of Parkinson's Disease: Clinical Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 582.02/D14

Topic: C.03. Parkinson's Disease

Title: Deep brain stimulation battery decay of Activa PC neurostimulators; initial clinical data

Authors: *R. P. PATEL[1], R. J. DIPAOLA[2], S. F. DANISH[1], S. WONG[2], E. L. HARGREAVES[1];
[1]Div. of Neurosurg., [2]Neurol., Robert Wood Johnson Med. School, Rutgers Univ., New Brunswick, NJ

Abstract: Deep Brain Stimulation (DBS) is an established adjunct neurosurgical treatment for movement disorders. At the heart of the DBS system is the neuromodulation device. Medtronic's most recent Activa (PC) neurostimulator is purported to have a 2-5 year battery life. We have followed 27 Parkinson's patients implanted from January 2010 to December 2011, targeting the STN and powered by Activa PCs. Presently, more than half (14/27) have had their neurostimulators exchanged, while another ten (10/27) still retain their initial neurostimulator. The remaining (3/27) were lost to follow up. Thus, we have continuously tracked data from (20/27) implanted individuals, and the start and end data from an additional (4/27). Battery start values ranged from 3.08V to 3.17V with a mean value of 3.14V (sem .0039). Battery end values ranged from 2.22 (EOS) to 2.60V with a single outlier at 2.69V (performed prematurely due to incarceration status) with a mean value of 2.55V (sem .03). Battery life durations of those that crossed the ERI 2.60V value ranged from 2.12 years to 4.47 years with a mean value of 3.58years (sem .17). Of the neurostimulators that continue to perform, the present durations range from 3.47years to 4.18years with a mean value of 3.73years (sem .10). Examination of the plotted battery charge decay curves suggests a cubic spline best fit with an initial concave up followed by a concave down. The first upward concavity is characterized by a rapid decline from the respective start values to a leveling off value ranging from 2.95V to 3.0V occurring by the

end of the initial six months. The level plane occurs between the battery charge values of 2.95V to 2.88V, lasting from 6 months to 3.5 years dependent upon programmed neurostimulator parameters. The second downward concavity declines more rapidly as the battery runs down with durations of approximately a year. The initial upward concavity was fairly homogenous across curves, while the downward concavity was fairly heterogeneous fanning out to cross the 2.60V ERI threshold at different durations, dependent upon programmed neurostimulator parameters.

Disclosures: R.P. Patel: None. **R.J. DiPaola:** None. **S.F. Danish:** None. **S. Wong:** None. **E.L. Hargreaves:** None.

Poster

582. Therapeutics of Parkinson's Disease: Clinical Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 582.03/D15

Topic: C.03. Parkinson's Disease

Support: NIH Grant NS038681

Title: Effects of gm1 ganglioside administration on cognitive, motor, and sensorimotor functions in Parkinson's disease patients

Authors: *J. S. SCHNEIDER[1], C. YANG[2];
[1]Dept Pathol, Anat. & Cell Biol, Thomas Jefferson Univ., Philadelphia, PA; [2]Publ. Hlth. Sci., Pennsylvania State Univ., Hershey, PA

Abstract: A single center, double-blind, delayed start study was conducted to examine symptomatic and disease-modifying effects of GM1 ganglioside in Parkinson's disease (PD). Seventy-seven subjects with PD were randomly assigned to receive GM1 for 2.5 years (early-start) or placebo for 6 months followed by GM1 for 2 years (delayed-start). Seventeen matched PD subjects received only standard-of-care and were followed to obtain comparative information about disease progression. The primary outcome measure was change from baseline of the Unified Parkinson's Disease Rating Scale (UPDRS) motor scores. At 6 months, the early-start group had statistically significant improvement in UPDRS motor scores vs. a significant worsening of scores in the delayed-start group. The early-start group also showed a sustained benefit vs. the delayed-start group at the end of the study period. These results suggested that GM1 may have symptomatic and potentially disease modifying effects on PD. We now present secondary outcome data from this study that show additional effects of GM1 treatment on motor

and non-motor symptoms in PD patients. Subjects performed a number of cognitive tests (e.g., tests of auditory attention, verbal fluency, executive function, visuospatial learning and memory) and objective motor and sensorimotor integration tests (e.g. finger tapping, pronation/supination, sensorimotor tracking task) at baseline and at various time points during the course of the 2.5 year study. In support of data obtained with UPDRS ratings, early-start subjects showed significant early improvements in a number of motor function measures, compared to delayed-start and comparison subjects and maintained improvements throughout the study period. Delayed-start subjects improved after switching from placebo to GM1. Subjects receiving GM1 also showed improvements in some cognitive functions (e.g., visuospatial learning, verbal fluency) over time compared to the standard-of-care comparison subjects. These data provide further support for the use of GM1 ganglioside as a potential treatment for PD.

Disclosures: J.S. Schneider: None. **C. Yang:** None.

Poster

582. Therapeutics of Parkinson's Disease: Clinical Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.03. Parkinson’s Disease

Support: NIH R01 NS 084975

NIH R01 NS 75013

NIH R01 NS 70872

NIH K08 NS 52232

The Grainger Foundation

Title: Computational modeling of stimulation-evoked dopamine release recorded with fast scan cyclic voltammetry

Authors: *J. TREVATHAN[1], J. L. LUJAN[2], K. H. LEE[2];
[2]Neurologic Surgery, [1]Mayo Clin., Rochester, MN

Abstract: Background Maximizing long-term efficacy of deep brain stimulation (DBS), a surgical therapy for movement and psychiatric disorders, requires frequent adjustment of stimulation parameters to compensate for the dynamic and progressive nature of such disorders.

Recent animal studies suggest that therapeutic DBS is associated with specific changes in neurotransmitter concentration measurable by electrochemical techniques. Thus, neurochemical monitoring coupled with feedback control of stimulation is a promising mechanism for optimizing the balance between symptom reduction and stimulation-induced side effects during DBS. The objective of work was to characterize the non-linear and time-varying dynamics of electrical stimulation evoked neurotransmitter release across various animal models and thus provide an important step towards closed-loop control of DBS based on neurochemical feedback. **Methods** In a cohort of Sprague-Dawley rats the medial forebrain bundle was electrically stimulated while fast scan cyclic voltammetry was used to record evoked dopamine (DA) release in the caudate. In both a cohort of swine and a single non-human primate the substantia nigra pars compacta / ventrotegmental area was stimulated while DA release was recorded within the anterior caudate. The kinetics of single-pulse stimulation-evoked DA release was mathematically modeled and a least-squares fit used to extract unique features of release. These features were used to train artificial neural networks (ANN) to model the relationship between stimulation parameters and DA release. Model validation was performed by calculating the Pearson's correlation between predicted model responses and a set of stimulation-evoked responses not used for model training. **Results** The mathematical models of DA release kinetics were able to fit the stimulation-evoked releases recorded in rats, swine, and a non-human primate. The ANNs trained on features of the kinetic model were able to characterize the relationship between stimulation parameters and DA release. **Conclusions** In both small and large animal models the non-linear and time-varying dynamics of DA release can be mathematically described. Development of these models describing stimulation-evoked neurochemical release is an important step towards understanding neurotransmitter release in the context of DBS as well as developing novel stimulation paradigms and closed-loop DBS systems that improve therapeutic efficacy. **Funding** This work was supported by the National Institutes of Health NINDS (R01NS084975 award to JLL, and R01 NS 75013, R01 NS 70872, K08 NS 52232 awards to KHL), and The Grainger Foundation.

Disclosures: **J. Trevathan:** None. **J.L. Lujan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Boston Scientific. **K.H. Lee:** None.

Poster

582. Therapeutics of Parkinson's Disease: Clinical Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 582.05/D17

Topic: C.03. Parkinson's Disease

Support: NSF CAREER-1351112

Utah Science, Technology, and Research Initiative

Title: Towards the implementation of a novel DBS electrode for targeted neural activation

Authors: *D. V. NESTEROVICH, A. WILLSIE, C. BUTSON, A. DORVAL;
Univ. of Utah, Salt Lake City, UT

Abstract: We have developed a novel electrode lead design for deep brain stimulation (DBS), a surgical intervention for several neurological disorders including Parkinson's Disease (PD). Our design, the micro DBS (μDBS), has 1760 electrode contacts, each with stimulation and recording capabilities. The organization of the contacts allows control over the size, shape, and direction of the induced electric field to fit the target area of stimulation without stimulating nearby tissue. The plus-shaped cross-section of the μDBS results in an 80% reduction in volume compared to existing clinical DBS electrodes, which decreases damage to the brain during lead placement. Despite these advantages, it is far easier to program manually the 4 contacts on conventional DBS leads than to determine optimal stimulation parameters for 1760 contacts. For the μDBS to gain acceptance, determination of parameter settings must be automated. Given an anatomical target area of stimulation, we seek an optimization method that will determine the most appropriate active contacts to generate neural activation within the target. To ensure the optimal treatment through the novel electrode in a patient-specific manner, the target area must be precisely defined within each patient. A 3D rendering of the subcortical target area will be derived from patient MRI data. Electric fields will be modeled through a finite element model of the μDBS with tissue conductivities derived from diffusion tensor imaging (DTI). The model will be created in SCIRun, a computational modeling package developed by the SCI Institute, and be used to calculate the volume of tissue activated for various contact configurations. We will use the Hessian matrix of second spatial partial derivatives, generated from an ideal scenario of target activation and manipulated through Newtonian optimization methods, to converge upon optimal contact configurations. This iterative algorithm will maximize percentage of target stimulated while minimizing stimulation outside the target. Combining this optimization process with the novel electrode may improve treatment for PD and enable symptom alleviation for a wide range of neurological conditions not presently treated with DBS.

Disclosures: **D.V. Nesterovich:** None. **A. Willsie:** None. **C. Butson:** None. **A. Dorval:** None.

Poster

582. Therapeutics of Parkinson's Disease: Clinical Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 582.06/D18

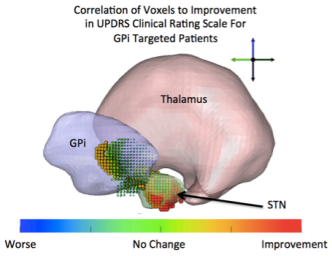
Topic: C.03. Parkinson's Disease

Support: NIH Grant NR-014852

Title: Identification of Deep Brain Stimulation targets from a cohort of Parkinson's disease patients

Authors: *G. DUFFLEY[1,2], D. CHEN[3], K. FOOTE[4,6], M. OKUN[5,6], C. R. BUTSON[1,2]; [1]Bioengineering, Univ. of Utah, Salt Lake City, UT; [2]Scientific Computing and Imaging (SCI) Inst., Salt Lake City, UT; [4]Neurosurg., [5]Neurol., [3]Univ. of Florida, Gainesville, FL; [6]Ctr. for Movement Disorders and Neurorestoration, Gainesville, FL

Abstract: Introduction: Deep Brain Stimulation (DBS) is an established treatment for Parkinson's Disease (PD). Our goal in this study is to identify stimulation target(s) across a cohort of PD patients with DBS leads implanted in the subthalamic nucleus (STN) or internal segment of the globus pallidus (GPi). Materials and Methods: Our cohort consisted of 52 PD patients who received unilateral DBS, 23 in GPi and 29 in STN. Clinical improvement was measured as the difference in Unified Parkinson's Disease Rating Scale (UPDRS) scores from pre-surgical baseline to 4 months after surgery. We used a previously published computational approach to predict the effects of DBS in each patient and build a probabilistic atlas of regions associated with therapeutic effects. All voxels included in analysis were stimulated in at least three patients. Results and Discussion: We observed variability in lead location among subjects in this cohort. The standard deviation in lead locations for STN DBS were: 1.568 mm along the medial-lateral axis; 2.103 mm along the anterior posterior axis; 2.046 mm along the dorsal-ventral axis. In turn, this resulted in differential activation of subregions around the surgical targets (STN and GPi). Among STN patients we observed regions where stimulation was associated with a mean improvement of 7.67 points on total UPDRS (total range of scores ranged from -6.33 to 24.33). Interestingly, we observed that the GPi patients with the best outcomes were those who were also stimulated in the STN (Figure 1). Conclusions: Our results combine computational models and clinical outcomes across a cohort of PD patients to identify regions where stimulation is correlated with improvement or worsening as measured using UPDRS. These results provide predictions of outcomes that can be prospectively tested in future patients. References: Butson, C. R., Cooper, S. E., Henderson, J. M., Wolgamuth, B., & McIntyre, C. C. (2011). Probabilistic Analysis of Activation Volumes Generated During Deep Brain Stimulation. NeuroImage, 54, 2096-2104.



Correlation of Voxels stimulated with change in UPDRS rating score: The high end of the color bar indicates a change of +12 in the UPDRS score at 4 months over baseline. The low end of the color bar indicates a change of -12, which indicates the patient actually performed worse. On average, the GPi targeted patients had a mean in change in score of -.10, and a standard deviation of 5.80.

Disclosures: G. Duffley: None. **D. Chen:** None. **K. Foote:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Device Donations from Medtronic and NeuroPace. **M. Okun:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH, NPF, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, the Bachmann- Strauss Foundation, the Tourette Syndrome Association, and the UF Foundation. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); royalties for publications with Demos, Manson, Amazon, Smashwords, Books$Patients, and Cambridge (movement disorders books. F. Consulting Fees (e.g., advisory boards); National Parkinson's Foundation. **C.R. Butson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); is an inventor of several patents related to neuromodulation therapy. F. Consulting Fees (e.g., advisory boards); . Butson has served as a consultant for Intelect Medical, NeuroPace, Advanced Bionics, St. Jude Medical, Boston Scientific and Functional Neuromodulation.

Poster

582. Therapeutics of Parkinson's Disease: Clinical Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 582.07/D19

Topic: C.03. Parkinson’s Disease

Title: Activity based interventions for individuals with Parkinson’s disease: An occupationally focused systematic review

Authors: *K. A. PICKETT, R. N. MASSART, K. J. LATHROP, A. MALSCH, S. E. GOLOFF;
Univ. of Wisconsin - Madison, Madison, WI

Abstract: Parkinson disease (PD) is a chronic neurodegenerative disease characterized by both motor and non-motor dysfunction. Along with the well known motor symptoms of tremor, bradykinesia, rigidity, and postural instability, depression, sleep disruption, cognitive changes, digestive system problems and falls are also prevalent. Exercise of both the group and individual types have been repeatedly shown to positively affect some of these symptoms; however, the exercise approaches, research designs and quality of results has varied greatly across studies. From the clinical perspective, discerning which avenues of intervention are best suited for this population is vitally important. To this end, four areas of interest were isolated from the PD exercise literature: falls, social engagement, depression, and activities of daily living. Methods. Using these topic areas, four systematic reviews were conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to search peer-reviewed literature using key search terms relevant to each content area. All searches excluded case studies and single subject designs. Results. Papers that met the inclusion criteria were isolated for each topic area: falls (n = 10), social engagement (n = 9), depression (n = 10), and activities of daily living (n = 7). Multiple types of interventions were shown to positively affect patient well-being. Additionally, several pharmacological interventions reported side effects, which may have reduced the treatment effect. Discussion. Findings indicate that while there is a plethora of research in this general area, many of the studies have been under powered, did not properly match groups or failed to properly control for systematic biases. The current body of literature reveals several areas of need for research. Additionally, it is clear from the summed collection of studies that rehabilitation therapists (Occupational and Physical Therapists) have a broad set of methodologies to consider as possible avenues for intervention. Future clinical intervention designs should strive to create change for individuals with PD by implementing interventions which are meaningful and effective for the individual.

Disclosures: K.A. Pickett: None. **R.N. Massart:** None. **K.J. Lathrop:** None. **A. Malsch:** None. **S.E. Goloff:** None.

Poster

582. Therapeutics of Parkinson's Disease: Clinical Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 582.08/D20

Topic: C.03. Parkinson’s Disease

Title: Anti-neuroinflammation effect of Zonisamide in early Parkinson's disease

Authors: *T. TERADA[1,2,6], M. YOKOKURA[3], E. YOSHIKAWA[7], M. FUTATSUBASHI[7], S. KONO[4], T. KONISHI[4], T. BUNAI[5], Y. HOSOI[4], M. SAKAO-SUZUKI[4], H. MIYAJIMA[4], Y. OUCHI[2];
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Abstract: *Introduction:* Previous animal studies have indicated that a new anti-PD drug Zonisamide (ZNS) may have a neuroprotective effect on neuroinflammatory process occurring in Parkinson's disease (PD). To evaluate this ZNS neuroprotective effect in humans, we examined changes in microglial activation prior to and after ZNS treatment in early-stage PD patients using [^{11}C]-DPA713 PET. *Methods:* Eleven PD patients (mean age 68.1±7.1) at Hoehn and Yahr (HY) stage 1~2 without dementia (Mini-Mental State Examination>23) or depression (normal Self rating Depression Scale) and age-matched controls underwent [^{11}C]-DPA713-PET measurements. We divided PD patients into two groups: PD with ZNS and PD without ZNS. All patients were followed-up and the second PET scan was performed one year later. The binding potential (BP_{ND}) was estimated using simplified reference tissue model. Statistical Parametric Mapping was used to compare regional BP_{ND} levels between the PD and control groups. To examine the ZNS effect on BP_{ND}, we compared the BP_{ND} increase between PD with and without ZNS groups using regions of interest analysis. *Results:* Significant increases of [^{11}C]-DPA713 BP_{ND} were found at the somatosensory parietal cortex in the HY stage 1 PD group and over the extensive brain regions in the HY stage 2 PD group. [11C]-DPA713 BP_{ND} at the second PET scan in the PD without ZNS group was significantly increased in the amygdala, anterior cingulate cortex, caudate, putamen, thalamus, posterior cingulate cortex, superior and middle frontal cortex, and parietal cortex, although PD with ZNS group did not show significant differences. *Conclusion:* These results indicated that microglial activation proceeds unilaterally as parkinsonism worsens during the early stage (HY 1 to 2) in PD. During this stage, ZNS treatment might be effective in reducing the neuroinflammation in PD.

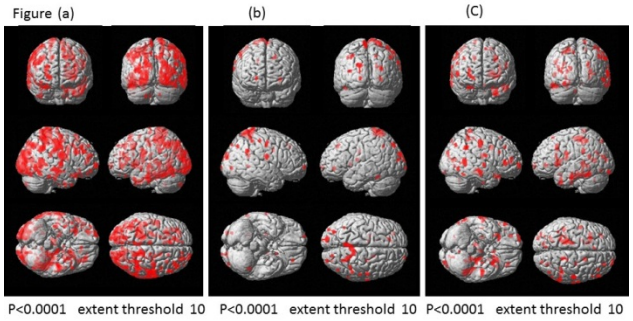

Figure legend
The regions of statistically significant increase in [11C]DPA binding potential (a) in Parkinson's disease patients group compared to age-matched controls group, (b) in Parkinson's disease patients at a Yahr 1 stage group compared to controls group, and (c) in Parkinson's disease patients at a Yahr 2 stage group compared to controls group (p<0.0001, uncorrected, extend threshold 10).

Disclosures: **T. Terada:** None. **M. Yokokura:** None. **E. Yoshikawa:** None. **M. Futatsubashi:** None. **S. Kono:** None. **T. Konishi:** None. **T. Bunai:** None. **Y. Hosoi:** None. **M. Sakao-Suzuki:** None. **H. Miyajima:** None. **Y. Ouchi:** None.

Poster

582. Therapeutics of Parkinson's Disease: Clinical Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 582.09/D21

Topic: C.03. Parkinson's Disease

Support: Hartman Foundation for Parkinson's Disease

Title: Can individuals with Parkinson's disease perceive complex auditory cues to correct movement?

Authors: ***T. PINKHASOV**[1], E. VASUDEVAN[2], M. SCHEDEL[3], D. WEYMOUTH[3], J. LOOMIS[3], L. MURATORI[4];
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Abstract: Gait disturbances are a characteristic feature of Parkinson's disease (PD) and are some of the most debilitating aspects of the illness. Current pharmacological treatments are ineffective at improving gait, but therapies that utilize different modalities to provide external cues to initiate and maintain movement have shown promise. Auditory cues in particular have been successful at improving gait speed and step variables. Recently this work has extended into the use of music as a cue for the rhythmical components of gait. A recent area of investigation in our

lab is the creation of personalized prolonged musical cues to correct gait deviations and prevent freezing and falls in persons with PD. The goal of the present study is to investigate the ability of individuals with PD to perceive auditory distortions and correct those distortions imbedded in different musical pieces. Data collection includes data from twenty individuals with PD and twenty healthy, age-matched peers. Participants listen to three pieces of music from three different genres (classical, rock, jazz) until they feel they are familiar with the music. Using a specifically developed iPad application, three different distortions are separately superimposed on each song creating nine possible combinations of sounds (i.e., song 1-3 x distortion 1-3). Participants listen to each of these in a random order for three trials for a total of 27 experimental trials. Participants manipulate a slide bar, the range of which corresponds to a randomly generated distortion "curve" with varying amounts of distortion but only one point of zero distortion. Participants are told they can take as much time as necessary to find that point of no distortion on each trial. The error between the level of distortion recorded and true zero is recorded. Our results show that individuals with PD have greater error than healthy individuals when correcting sound distortions ($p<0.01$ collapsed across conditions) but all participants were able to calibrate the songs to a very low level of distortion. In addition, there was an effect of song and distortion such that error correction was differentially effected by type of song and/or distortion for both healthy and persons with PD. The results suggest that music distortion can be used as a means of providing information about movement errors to people with PD. However, the type of music and distortion will impact the ability to optimize performance.

Disclosures: T. Pinkhasov: None. **E. Vasudevan:** None. **M. Schedel:** None. **D. Weymouth:** None. **J. Loomis:** None. **L. Muratori:** None.

Poster

582. Therapeutics of Parkinson's Disease: Clinical Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 582.10/D22

Topic: C.03. Parkinson's Disease

Support: Medtronic provided the firmware and equipment.

Title: Research firmware for deep brain stimulation devices: a randomized, blinded pilot study of novel stimulation patterns and shapes in Parkinson's disease and Essential Tremor

Authors: *U. AKBAR[1], R. S. RAIKE[2], N. HACK[3], C. HESS[4], J. SKINNER[5], D. MARTINEZ[4], S. DEJESUS[4], M. S. OKUN[4];
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Minneapolis, MN; [3]US Naval Hosp., Okinawa, Japan; [4]Neurol., [5]Univ. of Florida, Gainesville, FL

Abstract: The growing accessibility of deep brain stimulation (DBS) for movement disorders has made optimization of the technology a necessary next step. Traditional DBS pulses are rectangular-shaped with a passive recharge and the pulses can be delivered at a selected frequency, amplitude and duration (pulse width). We sought to assess the tolerability, effectiveness and efficiency of non-conventional DBS settings in Parkinson's disease (PD) and essential tremor (ET) patients. A randomized and blinded pilot study was performed using clinical rating assessments (Unified Parkinson's Disease Rating Scale, Tremor Rating Scale) and quantitative measures of motor function (accelerometer for tremor and bradykinesia, Peg board test, Timed Up-and-Go test, and GaitRite walking assessment). The study was a comparison of DBS subjects in the clinically optimized stimulation settings versus several non-conventional DBS settings, including: a biphasic pulse tested at and 30% below the clinical voltage; the traditional pulse at an irregular frequency with a coefficient of variance of 20%, tested at and 30% below the clinical voltage; 50% lower pulse width, tested at and 50% higher than the clinical voltage. Energy-consumption of all non-conventional settings was calculated and compared. Eleven subjects (8 PD and 3 ET) were tested and had a mean age of 62 years (range 47 to 75 years) and the mean disease duration for PD subjects was 11 years (range 8-18 years) and for ET subjects was 20 years (range 6-40 years). STN (n=7) was the most common target, followed by VIM (n=3), then GPi (n=1). Comparison with DBS-off and clinically optimized settings revealed that most non-conventional settings were effective, with one setting clearly eclipsing clinical settings over the optimized clinic setting (square biphasic pulse). The novel biphasic waveform setting captured tremor which had been under incomplete control in some subjects. Energy-consumption of the non-conventional settings was variable. This randomized, blinded pilot study investigated the effectiveness and efficiency of non-conventional settings utilizing clinical rating scales and quantitative measures in a clinic outpatient environment. Many of these settings were well-tolerated effective and efficient in PD and ET subjects. The biphasic waveform has potential clinical utility to provide symptom-specific relief in select patients who do not respond maximally to the commercially-available settings. The adoption of these non-conventional settings into clinical practice and the potential for updating the firmware on an already-implanted DBS device are appealing practice solutions and require further exploration.

Disclosures: **U. Akbar:** None. **R.S. Raike:** A. Employment/Salary (full or part-time):; Employed by Medtronic.. **N. Hack:** None. **C. Hess:** None. **J. Skinner:** None. **D. Martinez:** None. **S. DeJesus:** None. **M.S. Okun:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH, NPF, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, the Bachmann-Strauss Foundation, the Tourette Syndrome Association, and the UF Foundation. F. Consulting Fees (e.g., advisory boards); National Parkinson Foundation. Other;

royalties for publications with Demos, Manson, Amazon, Smashwords, Books4Patients, and Cambridge.

Poster

582. Therapeutics of Parkinson's Disease: Clinical Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 582.11/D23

Topic: C.03. Parkinson's Disease

Support: MJFF grant 199/2310

Title: Serotonin 5HT2A receptors in patient with Parkinson's disease with visual hallucinations

Authors: *S. CHO[1,2], A. STRAFELLA[1,2], M. CRIAUD[1], C. LI[1], M. ZUROWSKI[3], S. DUFF-CANNING[2], A.-C. VIJVERMAN[2], V. BRUNO[2], C. AQUINO[2], P. RUSJAN[1], S. HOULE[1], S. FOX[2];
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Abstract: Visual hallucinations (VH) are common in Parkinson's patients (PD) and are one of the strongest predictors of cognitive decline in PD. Central 5-HT system may have significant implication for understanding VH and cognitive/behavioral changes in PD with VH. The aim of this study was to investigate the association of the cognitive/behavioral changes of those PD patients who developed VH with the serotonergic system using PET measurement of cortical bindings of [18F]setoperone, a high-affinity antagonist of the 5-HT2A receptors. In total, 19 PD patients (8 PD without VH and 11 PD with VH) underwent PET scan. Individual binding potential (BP) map was calculated using the simplified reference tissue model using the cerebellum as a reference after the frame-based motion correction in each participants. Image preprocessing and statistical analysis were conducted with SPM 8. No statistically significant differences were found for clinical features except hallucination-subscore ($F= 20.5$, $P < 0.001$). In patients with VH, there was significant negative correlation between hallucination subcore and total MoCA score ($r = -0.61$, $P < 0.05$), indicating that higher level of hallucinations is directly related with lowered level of overall cognitive function in this patients group. We did not find any significant correlation between level of hallucination and BDI ($r = -0.01$, $P = 0.97$). Comparison between PD with and without VH disclosed several brain regions with BP differences in [18F]setoperone. VH group appears to be reliant on decreased BP in the right insula, bilateral dorsolateral prefrontal cortex, right orbitofrontal cortex, right middle temporal gyrus and right fusiform gyrus, thus suggesting significant abnormalities in 5-HT2A receptor

binding in these patients. In summary, in PD patients with VH, 5-HT2A receptor availability seemed to be affected in associative regions in the prefrontal and temporal cortex, thus possibly suggesting an abnormal functioning of those regions associated with cognitive and visual processing.

Disclosures: S. Cho: None. **A. Strafella:** None. **M. Criaud:** None. **C. Li:** None. **M. Zurowski:** None. **S. Duff-Canning:** None. **A. Vijverman:** None. **V. Bruno:** None. **C. Aquino:** None. **P. Rusjan:** None. **S. Houle:** None. **S. Fox:** None.

Poster

582. Therapeutics of Parkinson's Disease: Clinical Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 582.12/D24

Topic: C.03. Parkinson's Disease

Support: R01 NS 75013

R01 NS 70872

U Grant

National Institutes of Health NINDS

The Grainger Foundation

Title: The use of WINCS and Diamond electrode to perform wireless neurotransmitter monitoring in a patient with Parkinson's disease

Authors: *M. A. BABU[1], S. PAEK[2], P. MIN[2], C. BLAHA[2], J. TOMSHINE[2], M. MARSH[2], D. JANG[3], S.-Y. CHANG[2], K. BENNET[2], K. LEE[2];
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Abstract: Introduction: Prior work demonstrated that neurochemical monitoring can be performed during deep brain stimulation (DBS) using carbon fiber microelectrodes (CFM) and the Mayo-developed Wireless Instantaneous Neurotransmitter Concentration Sensing (WINCS) system. However, CFMs lack the durability to provide long-term neurochemical recording. Here, we demonstrate use of WINCS and diamond electrode-based electrochemical recording in Parkinson's disease patients. Methods: Mayo Clinic IRB approval was obtained for these studies.

Parkinson's disease patients were evaluated and approved for DBS neurosurgery by the Mayo Clinic DBS Committee. WINCS recordings were obtained during frame-based stereotactic DBS neurosurgery for Parkinson's disease. Diamond-coated microelectrodes were placed 2 mm anterior to the trajectory of the DBS electrode, which was placed in the subthalamic nucleus (STN). PPV was applied at 5 Hz (200 ms between two binary pulse sweeps), 400 V/s sweep rate, with respect to a reference electrode, from -0.4 V to 1.5 V back to -0.4 V. Results: Utilizing the novel diamond microelectrode, we were able to perform intra-operative neurochemical recordings. Oxidation peaks that were consistent with adenosine were observed when the electrode was implanted, advanced, removed, and when the DBS lead was advanced. Interestingly, tremor activity monitored by wireless accelerometer was abolished during lead insertion and was associated with putative adenosine release. No complications in the patient were observed intra-operatively or post-operatively. Conclusion: Diamond-coated microelectrodes in conjunction with WINCS can provide unique neurochemical information at the site of DBS lead placement. These novel technologies may facilitate our understanding of neurochemistry's role in brain function as well as help to elucidate the mechanism of DBS action. Acknowledgement: This work was supported by the National Institutes of Health NINDS (R01 NS 75013, R01 NS 70872, U), and The Grainger Foundation.

Disclosures: **M.A. Babu:** None. **S. Paek:** None. **P. Min:** None. **C. Blaha:** None. **J. Tomshine:** None. **M. Marsh:** None. **D. Jang:** None. **S. Chang:** None. **K. Bennet:** None. **K. Lee:** None.

Poster

582. Therapeutics of Parkinson's Disease: Clinical Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 582.13/D25

Topic: C.03. Parkinson's Disease

Support: RD12/0019/0013

S2010/BMD-2336

Title: Human neural stem cell therapy in experimental Parkinson's disease: beyond the brain

Authors: A. NELKE[1,2], S. GARCIA-LOPEZ[1,2], A. MARTINEZ-SERRANO[1,2], *M. P. PEREIRA[3,2];
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Abstract: Introduction: Parkinson´s disease (PD) is characterized by the impairment and death of dopaminergic neurons (DAn) in the Substantia Nigra pars compacta (SNpc), however there are symptoms of the disease other than those derived from events in the brain that do not receive as much attention. There is evidence that early signs of PD may occur in the gastrointestinal tract up to 20 years before motor symptoms become apparent.In this study, we sought to characterize the gastrointestinal symptoms in the colon and examine inflammation in the cervical lymph nodes in MPTP-lesioned mice, with and without human dopaminergic transplants. Methods: Adult C57BL/6 mice were injected i.p. with MPTP.One week later, they received a transplant of human ventral mesencephalic hVM1 clone 32 (human neural stem cells, hNSCs), or buffer, in the striatum and from this point on they were given immunosuppressant treatment. Four months post-transplantation, tissue samples were collected, and processed for immunohistochemical studies and/or used for protein extraction. Results: DAn degeneration was observed upon treatment with MPTP along with TH+ cell loss in the SNpc by immunohistochemistry, and behavioral anomalies; both of these factors were alleviated by hNSCs transplant. Non-CNS, cervical lymph nodes and colon, histological samples were studied.In the former, there was an increase in size in MPTP-treated mice as well as an augmentation in mast cell density compared to buffer-treated mice; these were potentiated in stem cell-treated mice.In colon protein studies, β-III-tubulin expression decreased in mice treated with MPTP and in hVM1 cell-transplanted mice, there was a prevention of further degeneration. COX-2 and NFkB expression increased in all stem cell-treated mice compared to naïve animals, demonstrating an activation of inflammatory pathways. Conclusions: Cell replacement therapy is focused on brain neurodegeneration and amelioration of central neurological symptoms while little focus is put on peripheral symptoms including those stemming from the enteric nervous system. Our study shows that the MPTP model leads to DAn degeneration accompanied by behavioral deficits and other alterations that occur outside of the CNS which could possibly be related to the prodromal symptoms of PD. Among these, an increase in lymph node area and mast cell density, and colonic inflammation. Stem cell transplants alleviated DAn loss, but possibly also contributed to a larger lymph node size and mast cell content,in addition to modulating colonic inflammation. For translational purposes and potential early diagnosis, events other than those of brain pathology need to be taken into account

Disclosures: **A. Nelke:** None. **S. Garcia-Lopez:** None. **A. Martinez-Serrano:** None. **M.P. Pereira:** None.

Poster

582. Therapeutics of Parkinson's Disease: Clinical Studies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 582.14/D26

Topic: C.03. Parkinson's Disease

Support: NIH R01 NS052318

NIH R01 NS75012

Title: *In vivo* nigrostriatal changes associated with MAO-B inhibitor therapy in Parkinson's disease

Authors: R. G. BURCIU[1], *E. OFORI[2], P. SHUKLA[1], O. PASTERNAK[7], J. W. CHUNG[1], N. R. MCFARLAND[3,4], M. S. OKUN[3,5,4], D. E. VAILLANCOURT[1,3,6];
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Abstract: From previous functional magnetic resonance imaging (MRI) studies in Parkinson's disease (PD) we know that the motor-related activity of the posterior putamen (pPUT) is reduced compared to that of healthy controls. Recently, diffusion MRI studies of the posterior substantia nigra (pSN) revealed increased free water levels in PD. Moreover, we know that the selective monoamine oxidase type B (MAO-B) inhibitor rasagiline provides a good control of parkinsonian symptoms, and is considered a promising disease-modifying drug candidate for PD. Here, we sought to determine the extent to which functional and structural integrity of the nigrostriatal circuit differed between PD patients already receiving rasagiline as part of their treatment regimen (n = 16) and patients treated with other antiparkinsonian drugs (n = 18). We had PD patients and a group of age-matched controls (n = 18) perform a well-established precision grip task in the MRI scanner, and we collected additional clinical and diffusion MRI measures. Importantly, the two PD groups had similar disease duration and disease severity and all tests were performed after 14-hour withdrawal from medications. As rasagiline is known to act upon dopamine metabolism, our main hypothesis was that PD on rasagiline will have a higher blood-oxygen-level dependent (BOLD) fMRI signal in the pPUT and reduced levels of free water in the pSN as compared to PD on other drugs. Current results: 1) confirm previous studies, and show a reduction in putaminal activity and increase in nigral free water in both PD groups as compared to controls; 2) add to the existing literature by showing that nigral free water predicts putaminal activity in PD, and clinical measures such as bimanual coordination; 3) and show that the rasagiline group have significantly higher BOLD signal in the pPUT and lower free water levels in the pSN than PD on other drugs. Together, these preliminary findings provide the first neuroanatomical evidence to support the proposed disease-modifying effects of rasagiline in PD, and open new avenues for the inclusion of functional and diffusion MRI measures in prospective, placebo-controlled studies establishing its long-term neuroprotective properties.

Disclosures: **R.G. Burciu:** None. **E. Ofori:** None. **P. Shukla:** None. **O. Pasternak:** None. **J.W. Chung:** None. **N.R. McFarland:** None. **M.S. Okun:** None. **D.E. Vaillancourt:** None.

Poster

583. Dystonia and Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 583.01/D27

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Foundation for Dystonia Research (FDR)

Title: Neurophysiological assessment of synaptic plasticity in dyt11 dystonia

Authors: M. MALTESE[1,2], G. SCIAMANNA[1,2], G. MARTELLA[1,2], G. PONTERIO[1,2], A. TASSONE[1,2], R. E. GOODCHILD[3], *A. PISANI[4,1,5];
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Abstract: Myoclonus dystonia (MD, DYT11) is a severe, childhood-onset neurological disease characterized by myoclonic jerks and dystonia, often accompanied by comorbid psychological conditions or epilepsy. DYT11 is an autosomal dominant MD form, caused by paternally inherited loss-of-function mutations in the maternally imprinted *SGCE* gene, whose protein product (eScg) is widely expressed in cerebral cortex, basal ganglia and hippocampal neurons. No gross structural defects have been found in affected patients, and, indeed, the pathophysiology is still largely unknown. By using electrophysiological approaches, we investigated intrinsic synaptic properties of striatal neurons in a DYT11 dystonia mouse model. We found no significant changes in the intrinsic synaptic properties of either striatal medium spiny GABAergic neurons (MSNs) or cholinergic interneurons (ChIs) recorded from Sgce+/- mice, compared to control Sgce+/+ mice. Recent findings suggest a role of *SGCE* in the regulation of dopamine D2 receptor (D2R) expression. Therefore, we explored the responses to D2R activation in striatal cholinergic interneurons. D2R activation by quinpirole resulted in a physiological reduction of spontaneous tonic firing activity in both genotypes. Dopamine modulates striatal plasticity. Thus, we also investigated the expression of short and long-term synaptic plasticity in the striatum of both Sgce+/- and Sgce+/+ mice. While short-term synaptic

plasticity was unaffected, Sgce+/- mice exhibited a significant impairment of corticostriatal long-term depression (LTD), compared to wild-type littermates. These experimental data provide evidence in support of an impairment of dopamine transmission in Sgce+/- mice. Further investigation is required to clarify the synaptic mechanisms underlying such impairment.

Disclosures: **M. Maltese:** None. **G. Sciamanna:** None. **G. Martella:** None. **G. Ponterio:** None. **A. Tassone:** None. **R.E. Goodchild:** None. **A. Pisani:** None.

Poster

583. Dystonia and Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 583.02/D28

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH Grant R01 NS069936

NIH Grant R01 NS082296

Title: PRRT2 deficiency causes paroxysmal dystonia in mice

Authors: ***M. S. LEDOUX**, J. XIAO, Y. XUE, E. M. MARQUEZ-LONA, S. R. VEMULA; Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: *PRRT2* loss-of-function mutations have been associated with familial paroxysmal kinesigenic dyskinesia (PKD), infantile convulsions and choreoathetosis, benign familial infantile seizures, hemiplegic migraine, and episodic ataxia. Dystonia is the foremost involuntary movement manifest by patients with PKD. At present, there is no unanimity on the neuroanatomical substrates of dystonia and several other paroxysmal disorders of the CNS. *Prrt2*$^{fl/fl}$ mice were generated with KOMP-CSD knockout first, promoter driven, targeted ES cells which harbor a lacZ-loxP-neo cassette. X-Gal staining was used to define the temporal and spatial distribution of *Prrt2* expression. The lacZ-loxP-neo cassette was removed via crossing to Flp deleter mice and *Prrt2* simple KO mice were subsequently generated via crosses with Cre deleter mice. Mice were examined with blinded assessments of open-field behavior and a battery of sensorimotor tests. QRT-PCR showed that *Prrt2* is neuronally-restricted. In brain, the highest levels of *Prrt2* expression were noted in cerebellum, with significantly lower expression in cerebral cortex and striatum. Expression was reduced by 50% in *Prrt2*$^{+/-}$ mice and completely absent in *Prrt2*$^{-/-}$ mice. QRT-PCR was corroborated with Western blots using brain and liver tissue. Overall, X-Gal staining showed that *Prrt2* expression was minimal in cerebral cortex and

striatum at all developmental time points. The highest expression levels were seen in cerebellar cortex (granule cells), cerebellar nuclei, thalamus, and piriform cortex with moderate expression in hippocampus and brainstem. The majority of *Prrt2*$^{+/-}$ mice and all of the *Prrt2*$^{-/-}$ mice have exhibited behavioral arrests and semi-rhythmic seizure-like truncal movements by P7 that peaked at P11 to P13. By P10, *Prrt2*$^{-/-}$ and *Prrt2*$^{+/-}$ mice manifest overt PKD, mainly dystonic, with variable involvement of the trunk and limbs. All of the witnessed episodes have lasted less than 2 min and are quite similar to human PKD in terms of clinical features. The majority of paroxysmal events (seizures, dyskinesias, dystonia, and other) seen in *Prrt2*$^{-/-}$ and *Prrt2*$^{+/-}$ mice resolve by P20. In comparison to WT littermates, *Prrt2*$^{-/-}$ mice show reduced open-field activity prior to P14 and increased open-field activity after P16. The PKD model that we have generated has strong etiologic and face validity. The distinctive *Prrt2* expression patterns in mouse brain and our *Prrt2* mouse model with conditional potential provide a powerful platform for understanding the neuroanatomical framework of dystonia, paroxysmal dyskinesias, epilepsy and other paroxysmal disorders of the CNS.

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Poster

583. Dystonia and Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 583.03/D29

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Nell Johnson Research Acceleration Fund

P50NS037409-13

P01NS087997

Title: Cholinergic function in mouse models of DYT-TOR1A dystonia

Authors: *K. L. ESKOW JAUNARAJS, C. N. THOMPSON, D. G. STANDAERT;
Dept of Neurology, CNET, Univ. of Alabama-Birmingham, Birmingham, AL

Abstract: Cholinergic function in mouse models of DYT1 dystonia. Karen L Eskow Jaunarajs, Chelsea N Thompson, and David Standaert DYT1 dystonia is a hyperkinetic movement disorder that is due to a ΔGAG mutation in the gene *TOR1A*, encoding the protein torsinA. Several lines of evidence suggest that striatal cholinergic interneuron activity may be enhanced in DYT1

dystonia. Clinically, anticholinergic drugs are the most effective pharmacological treatments available for DYT1 and other types of dystonia. In animal models of DYT1 dystonia, electrophysiological recording of cholinergic interneurons indicates paradoxical excitation in the presence of D2 receptor agonists. To date, acetylcholine levels have not been measured *in vivo*. We used a DYT1 ΔGAG knock-in mouse model (DYT1 KI) to investigate whether a hypercholinergic striatal state exists using *in vivo* microdialysis. In a between-subjects design, male wild-type and DYT1 KI mice were implanted with striatal microdialysis probes and perfused with artificial cerebrospinal fluid containing 0, 10, 100 and 500 nM neostigmine in an escalating-dose paradigm. Samples were collected and analyzed for extracellular acetylcholine. Results showed that DYT1 KI mice had 10-fold higher baseline levels of striatal acetylcholine compared to littermate controls. Responses to neostigmine at each dose trended higher in DYT1 KI mice. Ongoing studies in mice with acetylcholine cell-specific knockout of the *dyt1* gene (Ch-DYT1-KO) will enable us to determine whether hypercholinergic activity is due to cell-autonomous torsinA dysfunction in cholinergic cells. Further investigation of cholinergic activity in these models is necessary in order to elucidate the precise mechanisms and consequences of elevated striatal acetylcholine activity in mice with mutations in the gene encoding for torsinA.
Support: Nell Johnson Research Acceleration Fund, NIH P50NS037409-13, NIH P01NS087997

Disclosures: K.L. Eskow Jaunarajs: None. **C.N. Thompson:** None. **D.G. Standaert:** None.

Poster

583. Dystonia and Parkinson's Disease

Location: Hall A

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Program#/Poster#: 583.04/D30

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH Grant R01 NS069936

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Dorothy/Daniel Gerwin Parkinson's Research Fund

Title: Gene expression profiling in CIZ1-deficient mouse cerebellum

Authors: *S. R. VEMULA, J. XIAO, M. S. LEDOUX;
Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: A missense mutation in *CIZ1* (c.790A>G, p.S264G) was linked to autosomal dominant cervical dystonia in a large multiplex Caucasian pedigree (OMIM- 614860, DYT23).

CIZ1 is a p21 (Cip1/Waf1)-interacting zinc finger protein, robustly expressed in brain, and plays a role in DNA synthesis at the G1/S cell-cycle checkpoint. A *Ciz1* gene trap KO mouse model (intron 1) was generated to examine the functional role(s) of CIZ1 in terminally-differentiated neurons and contributions of CIZ1 to DNA repair in the mammalian brain. Total RNA from mouse cerebellum was harvested from 8 adult *Ciz1*$^{-/-}$ mice and 8 age- and gender- matched WT controls. *Ciz1* expression was virtually absent in KO mice. Whole-genome gene expression data derived from the MouseWG-6 v2.0 Expression BeadChip (Illumina) was analyzed with GeneSpring^{TM}. The *t*-test statistic was used to identify significantly dysregulated genes. Ingenuity Pathway Analysis (IPA) was used to model differentially regulated molecular/cellular networks. Genes involved in cell morphology, cellular function and maintenance, cell death and survival, cell signaling, and cell cycle were up-regulated (≥ 1.5X). *Erdr1*, erythroid differentiation factor 1, which plays a role as a pro-apoptotic factor and acts via the ERK pathway, showed the highest up-regulation (1.93X, p = 9.64E-04). The top up-regulated network is involved in the inflammatory response, cellular growth and proliferation, and cell-to-cell signaling and interaction. Down-regulated genes (≥ 1.0X) are involved in cellular development, cell cycle, cellular growth and proliferation, gene expression, and cellular movement. Similarly, down-regulated networks include those related to cell-to-cell signaling and interaction, inflammatory response, cell cycle and cell-mediated immune response. Enriched KEGG pathways for up-regulated genes include olfactory transduction, metabolic pathways, regulation of action cytoskeleton, and ECM-receptor interaction. Enriched KEGG pathways for down-regulated genes include metabolic pathways, Wnt signaling, and calcium signaling. In aggregate, these data are compatible with the following: (1) CIZ1 plays a role in CNS development and cell-cycle control, (2) up-regulation of cell cycle genes may compensate for CIZ1 deficiency in our KO mouse model, and (3) pathogenic dystonia-associated *CIZ1* mutations may operate via gain-of-function.

Disclosures: **S.R. Vemula:** None. **J. Xiao:** None. **M.S. LeDoux:** None.

Poster

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Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Dystonia Medical Foundation Clinical Fellowship

NIH NS065701 and ORDR at NCATS

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Title: Altered resting state functional connectivity MRI in adductor-type laryngeal dystonia

Authors: *S. A. NORRIS[1], M. C. CAMPBELL[2], J. M. KOLLER[2], A. Z. SNYDER[2], J. S. PERLMUTTER[2];
[1]Neurol., [2]Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Introduction: Adductor laryngeal dystonia (ADLD) is a task-specific dystonia that causes altered voice quality and projection. In genetic and non-genetic forms of isolated dystonia, functional imaging data suggest abnormalities in the basal ganglia, primary sensorimotor cortex, cerebellum, SMA, and thalamus. Tasks and ongoing movement during image acquisition confound interpretation in many of these studies. Based on functional and structural imaging data in isolated dystonia (including laryngeal dystonia) we hypothesize that functional connectivity will be disrupted in resting state networks including cerebello-thalamo-cortical and cortico-basal ganglia-thalamic networks in those with ADLD. Methods: Resting-state BOLD scans (Seimens 3T Trio) were obtained from ADLD participants (N = 23) -with (N = 13) or without (N = 10) botulinum toxin injections- and controls (CTL, N = 23) matched for gender, age, handedness, and head movement. Participants with excessive movement were excluded from all analyses (ADLD = 4; CTL = 3). Seed based functional connectivity analyses focused on sensorimotor cortical regions, basal ganglia, and cerebellar regions. Between-group analyses of resting-state functional connectivity compared all ADLD and CTL participants. Fisher z-transformed correlation coefficients were extracted for significant seed-clusters and confirmed with Monte-Carlo simulation. Results: ADLD participants demonstrated significantly altered functional connectivity compared to controls. A caudate seed demonstrated increased correlation with ipsilateral somatosensory cortex and decreased correlation with cerebellar cortex. A cerebellar seed demonstrated weaker correlations with inferior frontal gyrus, insular cortex, somatosensory cortex, and caudate. A somatosensory cortex seed demonstrated weaker correlations between cerebellum, thalamus and increased correlation with caudate and inferior frontal gyrus. Conclusion: Data demonstrate altered functional connectivity in a-priori regions of interest in the somatosensory cortex, basal ganglia and cerebellum using resting state MRI data in those with ADLD. Resting state functional connectivity analyses reveal functional brain network changes associated with this task-specific dystonia.

Disclosures: S.A. Norris: None. **M.C. Campbell:** None. **J.M. Koller:** None. **A.Z. Snyder:** None. **J.S. Perlmutter:** None.

Poster

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Support: Allergan Research Grant

MITACs Research Grant

Title: Multi-sensor based biomechanical characterization of cervical dystonia determines optimal onabotulinumtoxinA treatment parameters

Authors: O. SAMOTUS, H. MORADI, F. RAHIMI, *M. S. JOG;
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Abstract: Background: Assessing cervical dystonia is challenging to accomplish visually as the complexity of CD involves variations in rhythm, velocity, amplitude, and direction. Individualizing focal therapy commonly results in a dosing regimen associated with mediocre relief of symptoms. Biomechanical sensors can be applied as an objective method to measure head and neck biomechanics and thus simplifies the ease of diagnosis and accurate selection of optimal onabotulinumtoxinA injection parameters. Objective: To simultaneously quantify torticollis and superimposed dynamic movements in multiple degrees of freedom in order to identify dystonic neck muscles for onabotulinumtoxinA focal therapy. Methods: 24 drug-naïve CD participants were injected with onabotulinumtoxinA at week 0, 16 and 32 and attended follow-up visits six weeks following a treatment. Clinical rating scales (TWSTRS and UDRS) and kinematic assessments were completed at all visits. Kinematic recordings involved an inclinometer positioned above the right ear and a goniometer at C2 and T2 spinal segments to capture severity of natural head and neck twisting in three degrees of freedom (DOF): rotational, lateral, and vertical tilts. Static posturing, measured as angular deviation from calibrated neutral head position, and dynamic movements measured by angular RMS amplitude were collected. Dosing and muscle selection were based on both kinematic data and clinician's experience. Results: Mean TWSTRS-total score significantly improved from study baseline to weeks 6 and 16 by 17.1% and 10.1%, respectively. Kinematics objectively isolated static head posturing (angular deviation > 5.5 degrees) from dystonic movements (angular RMS amplitude > 0.35 degrees). Participants who presented with static posturing at baseline displayed a reduction in severity by 42.0%, 12.3% and 18.4% in lateral, vertical, and rotational DOFs, respectively. Participants with dystonic movements showed a decrease in severity by 28.8%, 35.2%, and 23.1% in lateral, vertical, and rotational planes of motion. Conclusions: Kinematics provides an objective understanding of neck biomechanics and can easily identify hyperkinetic muscles for focal therapy.

Disclosures: **O. Samotus:** None. **H. Moradi:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Allergan. **F. Rahimi:** None. **M.S. Jog:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Allergan. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Allergan.

Poster

583. Dystonia and Parkinson's Disease

Location: Hall A

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Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: The Collaborative Center for X-linked Dystonia Parkinsonism (XDP) at MGH

Title: Analysis of TAF1 gene splice variants in fibroblasts and iPS cells-derived neural stem cells from patients with X-Linked Dystonia-Parkinsonism

Authors: J. DHAKAL, *N. ITO, W. T. HENDRIKS, N. WAKABAYASHI-ITO, C. A. VAINE, C. LIU, D. SHIN, K. SHIN, T. MULTHAUPT-BUELL, N. SHARMA, X. O. BREAKEFIELD, D. C. BRAGG;
Program in Neurosci., Massachusetts Gen. Hosp., Charlestown, MA

Abstract: Background X-linked Dystonia-Parkinsonism (XDP) is a neurodegenerative disease endemic to the Philippines. The pathogenic genetic lesion is unclear, but previous studies identified a disease haplotype consisting of (a) 5 single nucleotide changes, designated disease-specific sequence changes (DSC1,2,3,10,12) in a region containing the *TAF1* gene; and (b) an SVA-type retrotransposon insertion in intron 32 of *TAF1*. One study also identified a brain-enriched TAF1 variant, N-TAF1 that was decreased in XDP caudate relative to controls (Makino et al. 2007). However, it is not clear if this decrease in N-TAF1 expression occurred secondary to neurodegeneration, or if it may be a primary effect of genotype that could contribute to XDP pathogenesis. **Objective and Methods** The goal of this study was to compare expression of transcripts derived from exons 1-38 of *TAF1*, and of N-TAF1 in particular, in XDP vs. control cells. Fibroblasts were derived from 5 XDP patients and 5 unaffected family members as controls, reprogrammed to induced pluripotent stem cells (iPSCs), and re-differentiated into neural stem cells (NSCs). Genotyping was confirmed via PCR and Sanger sequencing. Neural

conversion was confirmed via immunostaining for nestin, Pax6, and Musashi. Relative expression of TAF1 transcripts was assessed by qRT-PCR using a panel of primers spanning the entire gene. **Results** All XDP cell lines were positive for all haplotype markers, including the SVA, whereas controls had wild-type sequences at all positions. Most TAF1 transcripts did not differ significantly in XDP vs. control cells. In fibroblasts, five TAF1 variants were significantly lower in patients vs. controls. The most significant changes involved transcripts incorporating exons around intron 32 bearing the SVA, as well as ones derived from exons 34-36. N-TAF1 is derived from an alternative exon, 34', in this same region, and it was not detectable in fibroblasts. As positive controls, N-TAF1 expression was confirmed at low levels in human neuroblastoma cells and at relatively high levels in RNA from multiple human brain regions. Transcripts differentially expressed in fibroblasts were also significantly different in NSCs, along with N-TAF1 and one additional transcript. Of all TAF1 variants, N-TAF1 showed the largest fold difference in expression between XDP and control NSCs. **Conclusions** XDP-related sequence variation in *TAF1* appears to affect expression of multiple transcripts. Neural-specific expression of N-TAF1 and decreased expression in XDP vs. control cells are consistent with previous reports and indicate that this cellular phenotype is not a secondary consequence of cell loss in the brain.

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Poster

583. Dystonia and Parkinson's Disease

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Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH/NIDCD R01DC012545 to KS

Foundation for Surgery Reg Worcester Research Fellowship Scholarship, Royal Australasian College of Surgeons to DK

Title: Voice tremor in spasmodic dysphonia: a multi-modal neuroimaging study

Authors: D. KIRKE, G. BATTISTELLA, M. CHOY, V. KUMAR, E. RUBIEN-THOMAS, *K. SIMONYAN;
Neurol., Mount Sinai Sch. of Med., New York, NY

Abstract: Spasmodic dysphonia (SD) is a primary focal dystonia affecting the laryngeal muscles during speech production. In one-third of patients, SD co-exists with voice tremor (SD/VT). While there has been recent progress in understanding brain functional and structural alterations in SD, the pathophysiological basis of VT remain less clear. The aim of this study was to examine structural and functional brain abnormalities in 20 SD vs. 20 SD/VT vs. 20 healthy controls (HV) using functional MRI (fMRI) during symptomatic speech production, voxel based morphometry (VBM) and diffusion tensor imaging (DTI). We found that, while both SD and SD/VT groups showed widespread increases of activation in the sensorimotor cortical regions, basal ganglia, thalamus and cerebellum, the SD/VT patients had additionally increased activity in the right fronto-temporo-parietal cortex and bilateral cerebellum. The differences between the SD and SD/VT groups were also observed at the structural level. SD patients showed distinct white matter abnormalities in the right genu of the internal capsule, which was in line with previous findings in these patients, whereas SD/VT patients exhibited white matter changes in the right thalamus and gray matter alterations in the postcentral gyrus, cerebellum and brainstem. These findings indicate that, compared to healthy subjects, SD and SD/VT patients share the same abnormalities of brain function and structure, possibly attributed to SD symptoms. On the other hand, VT appears to contribute additional brain abnormalities along the cerebello-thalamo-cortical pathway, which are not present in patients with isolated SD. As the debate on whether VT is an integrated part of SD or a stand-alone disorder continues, our data provide brain organizational evidence that VT is likely a co-occurring disorder rather than a sub-symptom of SD. This knowledge may be important for designing new therapeutic options targeting disorder-specific abnormalities in SD and SD/VT.

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Poster

583. Dystonia and Parkinson's Disease

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Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH Grant NS064046

Provost Fellowship, University of Southern California

Title: Vibratory feedback and visualizations increase muscle awareness and task performance in subjects with dystonia during a redundant, one-dimensional myocontrol task

Authors: *S. A. LIYANAGAMAGE[1], M. BERTUCCO[1], T. D. SANGER[1,2];
[1]Biomed. Engin., USC, Los Angeles, CA; [2]Children's Hosp. Los Angeles, Los Angeles, CA

Abstract: We have previously used scaled vibratory feedback on children with secondary dystonia, and have seen improvement in their motor function after one month of practice. We have also seen that scaled forms of vibration cause significant increases in muscle use without a significant increase in overall performance. However, we still do understand why vibration behaves in this manner. We decided to approach the problem from a different angle by looking into the world of coaching to find concepts that could be used in motor skill training. Upon extensive literature review and an ongoing survey, we have decided visualizations play an important role in motor skill improvement. We hypothesize that scaled vibration is sport coaching-like i.e. it is able to manipulate a person's limb movements indirectly by bringing awareness to those areas of the body that need to be changed. In order to translate this concept to the field of motor control, we designed a 5-block, unilateral myocontrol Fitt's Law experiment in which subjects manipulated their arm to control a cursor on the computer. The brachioradialis and FDI muscles contributed to cursor movement, while the ADM did not (we didn't tell this to the subjects). Blocks 1 and 3 were baseline measurement blocks where we conducted 10 sets of trials, each presenting 5 target sizes. In block 2, we placed a vibratory feedback device on their brachioradialis while they performed the same task. In block 4, we showed subjects a fist clenching/unclenching movement, and asked them to continue the task using this movement, with the expectation that their performance and muscle use would change significantly with this visualization added. Then, in block 5, we asked them to complete the task using the best movement they saw fit in order to test how they adapt their movements after the two interventions. Preliminary results show that vibration of the brachioradialis muscle is able to reduce overall movement time, while visualization causes an increase. However, it was seen that subjects were able to reach a significantly reduced movement time in block 5 by using a hybrid of the movement they were using in block 1 and the one they were taught in block 4. These results show we are able to use vibration and visualization to manipulate subjects to increase efficiency of movement. The study is ongoing, and we believe there is much to be learned using such a paradigm with regards to changes in muscle use in children with dystonia since the ability to bring awareness within a noisy muscle environment will prove extremely useful to them. We believe that this paradigm can aid in improving specific motor skills and overall performance.

Disclosures: S.A. Liyanagamage: None. **M. Bertucco:** None. **T.D. Sanger:** None.

Poster

583. Dystonia and Parkinson's Disease

Location: Hall A

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Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Title: Investigating premotor-parietal connectivity in writer's cramp patients

Authors: N. THIRUGNANASAMBANDAM, A. S. PILLAI, J. A. SHIELDS, *M. HALLETT; Human Motor Control Sec, NINDS/NIH, Bethesda, MD

Abstract: Patients with writer's cramp demonstrate task-specific dystonic symptoms of the hand during handwriting, while no symptoms are observed during other similar distal motor tasks. Recent studies postulate that impaired cortical connectivity could be partly responsible for the task specific symptoms. Functional MRI studies have shown that the left premotor and posterior parietal cortices are part of the task-specificity network. The resting state connectivity between these 2 regions and the connectivity during handwriting was decreased in WC patients on fMRI. The connectivity between premotor and parietal areas during handwriting has, however, not been explored with EEG. In the present study, we hypothesized that left premotor-parietal connectivity would be lower in writer's cramp patients than healthy controls during handwriting. We are currently recruiting writer's cramp patients and age- and sex-matched healthy controls for this study. We record 32-channel EEG while the participants performed one of the following tasks - handwriting or sharpening a pencil or imagining writing/sharpening. We calculate the task-related power (TR-Pow) and imaginary part of coherence (TR-ImCoh) between left premotor (FC5) and posterior parietal (P3) cortices. Our preliminary results show that alpha TR-Pow decreased for the actual motor tasks and increased for the imagination tasks in both subject groups. The alpha TR-ImCoh increased the most during writing in healthy controls, while it decreased in patients. This study confirms the fMRI results and can be further exploited to evaluate dynamic changes.

Disclosures: N. Thirugnanasambandam: None. **A.S. Pillai:** None. **J.A. Shields:** None. **M. Hallett:** None.

Poster

583. Dystonia and Parkinson's Disease

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Bachmann-Strauss Dystonia and Parkinson Foundation

Title: Genetic inducible silencing of cerebellar synapses in mice

Authors: *J. WHITE, R. V. SILLITOE;
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Abstract: The cerebellum is critical for several motor functions including coordination, learning, and balance. It is therefore not surprising that damaging the cerebellum impacts movement. However, while we are rapidly gaining a better appreciation for how the anatomical and molecular landscape is affected in cerebellar disorders, knowledge of how neuronal activity within the cerebellum is altered in motor disease is still poorly understood. To address this problem, we devised an approach to manipulate the different steps of signal processing in the cerebellum in order to determine how different synapses contribute to motor behavior. We have found that the silencing of Purkinje cell synapses, by removing vesicular GABA transporter from Purkinje cell axon terminals, disrupts the normal wiring and firing of the circuit, which ultimately leads to disequilibrium and ataxia. But, in order to disentangle the roles of the Purkinje cell from its surrounding microcircuit during motor processing, we stepped back a synapse to silence glutamatergic input into the cerebellar cortex. We accomplished this by removing vesicular glutamate transporter from presynaptic axon terminals in order to gain insight into the behavioral and pathophysiological role of afferents. We show using mouse behavior, high-resolution anatomy and *in vivo*, awake electrophysiology that constitutive loss of glutamatergic synaptic transmission leads to a very different behavioral phenotype compared to silencing the Purkinje cells themselves. Similar to our mice with silenced Purkinje cells, the mice with silenced afferent signaling show abnormal firing within the cerebellar circuit, but instead of disequilibrium and ataxia, these mice exhibit severe muscle co-contractions that impede normal movement. Our data suggest that loss of afferent neurotransmission leads to cortical processing errors that cause cerebellar nuclear neurons to fire with abnormal properties. We propose that multiple cerebellar cortical deficiencies might be corrected and motor function restored by therapeutically targeting the cerebellar nuclei.

Disclosures: J. White: None. **R.V. Sillitoe:** None.

Poster

583. Dystonia and Parkinson's Disease

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Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Fahn award of the Dystonia Medical Research Foundation to Pedro Gonzalez-Alegre

Title: TorsinA regulates adaptation to chronic stress *in vivo*

Authors: *G. BEAUVAIS[1], N. BODE[2], J. L. WATSON[1], H. M. WEN[3], K. A. GLENN[3], P. GONZALEZ-ALEGRE[4,5];
[1]Children's Hosp. of Philadelphia, Philadelphia, PA; [2]Dept. of Neurol., [3]Dept. of Med., Roy J and Lucille Carver Col. of Med. at the Univ. of Iowa, Iowa, IA; [4]Dept. of Neurol., Perelman Sch. of Med. at the Univ. of Pennsylvania, Philadelphia, PA; [5]Ctr. for Cell & Mol. Therapy, The Children's Hosp. of Philadelphia, Philadelphia, PA

Abstract: DYT1 dystonia is a disabling neurological that causes repetitive twisting involuntary movements. DYT1 is caused by a GAG deletion in the TOR1A gene encoding the endoplasmic reticulum (ER) resident AAA+ ATPase torsinA. The cellular function of torsinA remains unknown. Experimental evidence from several laboratories suggests that torsinA protects neurons under conditions of ER stress by assisting in the degradation of misfolded proteins via ERAD, and the ΔGAG mutation impairs this function. As a result, ER stress is a potential regulator of disease penetrance and severity. However, this hypothesis has never been tested in mammalian models *in vivo*. Here, we evaluated the behavioral, histological and biochemical consequences of chronic ER stress in DYT1 ΔGAG knock-in (KI) mouse model. P58IPK is an ER chaperone that binds to proteins being imported into the ER to promote proper folding. p58IPK-null mice are sensitive to ER stressors in different somatic tissues including pancreas and the gut, likely as a result of increased input of misfolded proteins. However, they do not exhibit brain abnormalities. Therefore, combining abnormal P58IPK and torsinA function might lead to increase input and reduced output of misfolded proteins from the ER, triggering a neurological phenotype. To test this hypothesis, we crossed DYT1 knock in (KI/+) with p58IPK (-/+) mice. We obtained the expected number of animals for all possible genotypes except for DYT1 (KI/+)/ p58IPK (-/-), suggesting a genetic interaction during development. However, behavioral evaluation of surviving animals did not show any abnormalities in behavior specific to that genotype. Protein analysis demonstrated activation of ER stress responses upon loss of p58IPK in cerebellum, striatum and cortex of 2-week and 9-month old mice. Interestingly, some changes were found to be age- and region-specific. Unbiased proteomic analysis through 2DIGE of brain lysates followed by MS/MS identification of dysregulated proteins indicated that combining torsinA and p58IPK dysfunction alters levels of proteins implicated in protein quality control pathways and calcium signaling. In sum, our findings suggest that torsinA might modify the neuronal response to chronic ER stress from embryonic development to adulthood.

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Poster

583. Dystonia and Parkinson's Disease

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Department of Defense

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National Science Foundation

Whitehall Foundation

Title: Enhanced glutamatergic synaptic transmission in a DYT1 dystonia mouse model, evaluated by membrane-potential imaging

Authors: *S. IWABUCHI, N. C. HARATA;
Dept. of Mol. Physiol. & Biophysics, Univ. of Iowa, Iowa City, IA

Abstract: Dystonia is a hyperkinetic movement disorder and is characterized by sustained or intermittent muscle contractions that cause abnormal repetitive movements and postures. Patients with dystonia are subject to increased brain excitability in the absence of apparent neurodegeneration. Thus, one of the main pathophysiological features of dystonia appears to be abnormal control of neuronal excitability, e.g. an imbalance in excitatory glutamatergic and inhibitory GABAergic synaptic transmission. However, to date we have only limited information about whether the excitability at the single-neuron level is affected in the absence of experimental manipulation of glutamatergic and GABAergic synaptic transmission. We have tested the net excitability of brain neurons of a dystonia model in the absence of antagonists of ionotropic glutamate and GABA receptors. Specifically, we prepared primary cultures of hippocampal neurons from a ΔE-torsinA knock-in mouse model of DYT1 dystonia, the most common form of inherited dystonia. We evaluated the excitability of these neurons following electric field stimulation, by imaging the membrane potential changes using a fluorescent indicator FluoVolt. In wild-type neurons, field stimulation led to an action potential, followed by 1) hyperpolarization lasting several 10's of ms, 2) no change in membrane potential, or 3) a small depolarization. All these responses were blocked by the Na^+-channel inhibitor tetrodotoxin,

suggesting that they were caused by action potentials. In some neurons, a stimulus-triggered action potential was followed by multiple action potentials, each preceded by slowly rising depolarization reminiscent of glutamate-mediated excitatory postsynaptic potentials (EPSPs). The latter responses were blocked by CNQX, an antagonist of AMPA-type ionotropic glutamate receptors. Thus we were able to identify the individual action potentials, depolarizing EPSPs and membrane hyperpolarization. Heterozygous mutant neurons more frequently exhibited depolarizing responses following stimulation than their wild-type counterparts, and these responses were blocked by CNQX. Our results demonstrate that glutamatergic synaptic transmission is enhanced in brain neurons of the DYT1 dystonia mouse model.

Disclosures: S. Iwabuchi: None. **N.C. Harata:** None.

Poster

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Support: NIH Grant R01 NS069936

NIH Grant R01 NS082296

Title: Role of major and brain-specific Sgce isoforms in the pathogenesis of myoclonus-dystonia syndrome

Authors: *J. XIAO, Y. XUE, S. R. VEMULA, M. S. LEDOUX;
Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: Loss-of-functions mutations in *SGCE* which encodes ε-sarcoglycan (ε-SG) cause myoclonus-dystonia syndrome (OMIM-159900, DYT11). The ubiquitous ε-SG protein (major isoform, 12 exons) and a brain-specific protein, derived from alternative exon 11b (13 exons), are reportedly localized in different synaptosomal membrane fractions: post- and pre-synaptic membrane, respectively. Moreover, deficiency of the brain-specific isoform may be central to the pathogenesis of DYT11. However, no animal model supports this hypothesis. Gene trapped ES cells (CMHD-GT_148G1-3, intron 10 -major isoform) were used to generate a novel *Sgce* mouse model with absent expression of both the ubiquitous and brain-specific isoforms of *Sgce* on the C57BL/6J background. In WT mouse brain, cerebellum showed significantly higher relative expression of the brain-specific isoform. Homozygotes ($Sgce^{-/-}$) and paternal heterozygotes

showed 60-70% reductions in expression of total *Sgce* (short isoforms preserved) although expression of the major and brain-specific isoforms was absent. Immunohistochemical assessments in WT mice using several ε-SG antibodies revealed punctate patterns of immunoreactivity of variable size, shape and density in motor regions of the CNS, with overall reductions in *Sgce*$^{-/-}$ mice. Genome-wide gene expression data using RNA derived from adult cerebellum showed moderate up-regulation of inflammatory response and moderate down-regulation of cell-to-cell signaling and interaction, cell death and survival, and cellular growth and proliferation genes in paternal heterozygotes. Over 50% of paternal heterozygote and *Sgce*$^{-/-}$ mice exhibited a variety of subtle motor abnormalities between P10 to P13. Abnormalities noted in older paternal heterozygote and *Sgce*$^{-/-}$ mice included reduced body weight, altered gait dynamics, and reduced open-field activity. Overt spontaneous or stimulus-sensitive myoclonus was not apparent on the C57BL/6J background. Our data suggests that short *Sgce* isoforms may compensate, in part, for deficiency of the major and brain-specific *Sgce* isoforms.

Disclosures: J. Xiao: None. **Y. Xue:** None. **S.R. Vemula:** None. **M.S. LeDoux:** None.

Poster

583. Dystonia and Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 583.15/D41

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Health Labour Sciences Research Grant in Japan

Title: The epidemiological and molecular analysis of Paroxysmal kinesigenic dyskinesia in Japan

Authors: H. TANGE[1], M. OHISHI[1], N. KUROTAKI[1], Y. MORIMOTO[1], S. ONO[1], Y. KUSUMOTO[1], S. YAMADA[1], K. SHIROTANI[3], N. IWATA[3], K. YOSHIURA[4], *N. MORI[2], H. OZAWA[1];
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Abstract: Paroxysmal kinesigenic dyskinesia(PKD) is characterized by recurrent, brief attacks of involuntary movement triggered by sudden voluntary movement. For example, patients often show dystonic movements in standing up suddenly, breaking into a run, and etc. The attacks more than one hundred times a day cause difficulties in daily life. Some PKDs are thought be

familial and others are sporadic. In 2011, PRRT2 on chromosome 16 is responsible for PKD reported by the Chinese group. A year later, our group found that the mutation is almost concentrated into c.649dupC (p.Arg217Profs*8) and involved in benign infantile seizure. Additionally, several reports show that PRRT2 is related to not only infantile seizure, but also migraine, and other epileptic disorders. The papers of both Wood H. in the Nat Rev Neurology (2012) and one of Scheffer IE.'s in the Nat Rev Neurology (2013) emphasized the PRRT2 gene in clinical neurology. In this situation, we proposed epidemiological study of PKD in Japan and have performed the molecular analysis to estimate the relationship between PKD and its complications. First, we conducted the survey by using a questionnaire about the frequency and the complications of PKD, and the medical treatments of the members of both Japanese Society of Neurology and Japanese Society of Child Neurology. Japanese Society of Psychiatry and Neurology kindly recommended the study. A total of all members are 6000 and the response rate of a questionnaire was about 50%. In this survey, 426 cases of PKD have reported by members of these societies. Interestingly, 147 cases had various complications including epileptic seizure, autistic disorders, bipolar disorders and other neurological disorders. Until now, we analyzed PRRT2 mutations in 60 cases resulting c.649dupC of PRRT2 is main gene alterations as reported previously. However, some cases have no mutation of PRRT2. We will perform further investigation utilizing the next generation sequence technology in the cases without any PRRT2 mutation. Otherwise, we are estimating clinical features of pure PKD and PKD with other complications combined with genotype of each case. Our study will show the genotype – phenotype correlation of PKD. Also, we could shed light on the molecular genetic aspect of neuropsychiatric diseases including autistic disorders, mood disorders based on the results of molecular analysis of PKD. This study received the ethical approval from the Committee for Ethical Issues in Human Genome and Gene Analysis at Nagasaki University, Japan. Also, this study is supported by Health Labour Sciences Research Grant.

Disclosures: H. Tange: None. **M. Ohishi:** None. **N. Kurotaki:** None. **Y. Morimoto:** None. **S. Ono:** None. **Y. Kusumoto:** None. **S. Yamada:** None. **K. Shirotani:** None. **N. Iwata:** None. **K. Yoshiura:** None. **N. Mori:** None. **H. Ozawa:** None.

Poster

583. Dystonia and Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 583.16/D42

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: MRC Studentship

Title: ε-sarcoglycan interacts with components of the dystrophin-associated glycoprotein complex and other membrane proteins in the brain

Authors: F. A. CARLISLE[1], A. J. WAITE[1], Y. CHAN[3,4], *A. R. ISLES[2], D. J. BLAKE[1]; [1]MRC CNGG, [2]Cardiff Univ., Cardiff, United Kingdom; [3]Ultragenyx Pharmaceut. Inc., Novato, CA; [4]McColl-Lockwood Lab. for Muscular Dystrophy Res., Carolinas Med. Ctr., Charlotte, NC

Abstract: Mutations in SGCE, which encodes the membrane glycoprotein ε-sarcoglycan, cause a form of the neurogenic movement disorder myoclonus-dystonia syndrome (MDS). However, mutations in the genes encoding the related α-, β-, δ- and γ-sarcoglycans cause limb-girdle muscular dystrophy (LGMD). LGMD patients have no reported MDS-associated symptoms, while MDS patients have no muscle pathology. In muscle, the sarcoglycans form a sarcolemmal heterotetrameric complex that is a subcomplex of the dystrophin-associated glycoprotein complex (DGC) and is disrupted in LGMD. Differences in the composition of sarcoglycan complexes between brain and muscle could contribute to the lack of neurological symptoms in LGMD patients; therefore we carried out immunoaffinity purification of ε-sarcoglycan from rodent brain to identify components of ε-sarcoglycan-containing complexes. We found that brain ε-sarcoglycan isoforms co-purified with β-, δ- and ζ-sarcoglycan as well as other DGC components and further membrane proteins. In addition, a direct interaction between ε-sarcoglycan and ζ-sarcoglycan was detected *in vitro* and in the SGCD mutant BIO14.6 hamster. These results indicate that ε-sarcoglycan is part of a prototypical sarcoglycan complex in brain, but may also form non-canonical complexes with ζ-sarcoglycan and other proteins. This variation in the composition of brain ε-sarcoglycan-containing complexes may contribute to the distinct phenotypes of sarcoglycan-related LGMD and MDS.

Disclosures: F.A. Carlisle: None. **A.J. Waite:** None. **Y. Chan:** None. **A.R. Isles:** None. **D.J. Blake:** None.

Poster

583. Dystonia and Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 583.17/D43

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: RO1NS077730

Title: Abnormal twisting movements and selective loss of maturing striatal cholinergic interneurons in forebrain-conditional Tor1a knockout mice

Authors: *S. S. PAPPAS, W. T. DAUER;
Dept Neurol., Univ. of Michigan, Ann Arbor, MI

Abstract: Dystonia is a movement disorder characterized by prolonged involuntary twisting movements. Abnormal basal ganglia function is implicated as a key cause of dystonic movements, but the cellular basis for striatal dysfunction remains undefined. DYT1 dystonia, the most common inherited form of primary dystonia, is caused by a dominantly inherited loss of function mutation in the TOR1A gene (encoding the protein torsinA). We modeled dystonia-related neuronal dysfunction in forebrain motor circuits by conditionally deleting torsinA from forebrain GABAergic and cholinergic neurons (Dlx5/6 - Tor1a conditional knockout mice - "Dlx-cKO"). Similar to DYT1 subjects, Dlx-cKO mice exhibit abnormal twisting movements that emerge during juvenile CNS maturation. These dystonic-like movements coincide with the exclusive degeneration of striatal cholinergic interneurons, predominantly in the dorsolateral motor region. Moreover, the abnormal movements are reduced by the same antimuscarinic treatment used clinically, highlighting the predictive validity of the model. We are examining cell and circuit level abnormalities in surviving cholinergic neurons to determine the mechanism whereby anticholinergic compounds rescue a phenotype characterized by loss of cholinergic neurons, and to understand the molecular basis for the selective loss of dorsolateral striatal interneurons during neurodevelopment. This behaviorally symptomatic mouse model of dystonia provides a powerful platform for identifying specific circuits and cell types that drive abnormal motor function in DYT1 dystonia.

Disclosures: S.S. Pappas: None. **W.T. Dauer:** None.

Poster

583. Dystonia and Parkinson's Disease

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Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH/NINDS P50 NS037409

NIH/NINDS R15 NS078728

DOD W81XWH-12-1-0380

Bachmann-Strauss Dystonia&Parkinson Foundation

Dystonia Medical Research Foundation

Title: A *Drosophila* model of human DYT1 dystonia

Authors: *N. WAKABAYASHI-ITO[1], R. R. AJJURI[2], B. W. HENDERSON[2], O. M. DOHERTY[2], X. O. BREAKEFIELD[1], J. M. O'DONNELL[2], N. ITO[1];
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Abstract: Dystonia represents the third most common movement disorder in humans with over 20 genetic loci identified. *TOR1A (DYT1)*, the gene responsible for the most common primary hereditary dystonia, encodes torsinA, an AAA ATPase family protein. Most cases of DYT1 dystonia are caused by a 3 bp (GAG) deletion that results in the loss of a glutamic acid residue (ΔE302/303) in the carboxyl terminal region of torsinA. This torsinAΔE mutant protein has been speculated to act in a dominant-negative manner to decrease activity of wild type torsinA. *Drosophila melanogaster* has a single torsin-related gene, *dtorsin*. Null mutants of *dtorsin* exhibited locomotion defects in third instar larvae. Levels of dopamine and GTP cyclohydrolase (GTPCH) proteins, which is encoded by *Punch*, were severely reduced in *dtorsin*-null brains. Further, the locomotion defect was rescued by the expression of human torsinA or feeding with dopamine. Here, we demonstrate that human torsinAΔE dominantly inhibited locomotion in larvae and adults when expressed in neurons using a pan-neuronal promoter Elav. Dopamine and tetrahydrobiopterin (BH_4) levels were significantly reduced in larval brains and the expression level of GTPCH protein was severely impaired in adult and larval brains. When human torsinA and torsinAΔE were co-expressed in neurons in *dtorsin*-null larvae and adults, the locomotion rates and the expression levels of GTPCH protein were severely reduced. These results support the hypothesis that torsinAΔE inhibits wild type torsinA activity. Similarly, neuronal expression of a *Drosophila* DtorsinΔE equivalent mutation dominantly inhibited larval locomotion and GTPCH protein expression. These results indicate that both torsinAΔE and DtorsinΔE act in a dominant-negative manner. We also demonstrate that Dtorsin regulates GTPCH expression at the post-transcriptional level. This *Drosophila* model of DYT1 dystonia provides an important tool for studying the differences in the molecular function between the wild type and the mutant torsin proteins.

Disclosures: N. Wakabayashi-Ito: None. **R.R. Ajjuri:** None. **B.W. Henderson:** None. **O.M. Doherty:** None. **X.O. Breakefield:** None. **J.M. O'Donnell:** None. **N. Ito:** None.

Poster

583. Dystonia and Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 583.19/D45

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH U54NS06571-03S1

Emory University Research Committee UL1 RR025008

Title: Functional imaging of head movements in healthy volunteers and in cervical dystonia

Authors: *C. N. PRUDENTE[1,2], R. STILLA[3], C. BUETEFISCH[3], T. KIMBERLEY[2], X. HU[3], K. SATHIAN[3], E. HESS[3], H. JINNAH[3];
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Abstract: Background: The neuroanatomical substrates for head movements in humans are not well delineated. It is not clear whether neck muscles are controlled by the ipsilateral or contralateral hemisphere, and the location of the neck region in the motor homunculus is still debated. This lack of information about normal head movements is relevant to cervical dystonia (CD), a disorder characterized by involuntary contractions of neck muscles. Current understanding of the neuroanatomical basis of CD is limited. We addressed the neuroanatomical substrates of head movements in normal individuals and in CD using functional magnetic resonance imaging (fMRI) and an isometric head task. Purpose: The experiments had two main goals: to delineate the neural basis for normal head movements in normal people and to identify abnormalities associated with CD. Methods: Scanning was conducted during isometric head rotation to the right or left. Isometric wrist extension with either hand was examined as a positive control condition. Electromyography recordings during scanning ensured compliance with tasks. Results: Seventeen healthy volunteers and 16 individuals with CD participated in the study. Isometric head rotation in healthy volunteers induced significant activation in the bilateral precentral gyrus, both medial and lateral to the hand area, as well as in the bilateral supplementary motor area, insula, putamen, and ipsilateral cerebellum. CD subjects had an overall broader activation of cortical and subcortical areas, except in the medial precentral gyrus. However, statistical comparisons failed to reveal significant differences between groups. Analyses of CD data normalized to the side of torticollis indicated that head tasks in the direction of abnormal movements were associated with more activation in the ipsilateral anterior cerebellum, whereas moving the head in the opposite direction involved more activity in sensory and motor cortical areas. Conclusions: The findings in healthy humans suggest that head movements are controlled bilaterally in the precentral gyrus. Furthermore, the results in CD subjects imply significant asymmetries of brain activity associated with the torticollic and non-torticollic directions of head movements.

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Poster

583. Dystonia and Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 583.20/D46

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH/NIDCD R01DC011805 to KS

Title: Distinct and shared patterns of resting-state functional connectivity alterations in task-specific and non task-specific primary focal dystonia

Authors: *G. BATTISTELLA[1], P. TERMSARASAB[1], R. RAMDHANI[1], K. SIMONYAN[2]; [1]Dept. of Neurology, Icahn Sch. of Med., New York, NY; [2]Dept. of Neurol. and Otolaryngology, Icahn Sch. of Med., New York, NY

Abstract: Although the task specificity in dystonia is a clinically well-defined phenomenon, its pathophysiology is poorly understood. In this study, we examined large-scale neural networks underlying the task specificity in dystonia by utilizing a two-tiered network analysis of multivariate independent component analysis (ICA) and graph theoretical analysis in patients with task-specific dystonia (15 TSD: writer's cramp and laryngeal dystonia), non-task specific dystonia (18 NTSD: cervical dystonia and blepharospasm) and healthy controls (15 HV). ICA was performed using the MELODIC tool in the FSL software; between-group differences in functional connectivity among the spatial components were assessed using a dual regression analysis and one-way ANOVA at a corrected $p \leq 0.05$. Graph analysis was performed using the Brain Connectivity Toolbox; 212-region whole-brain parcellation was applied to extract individual time series and construct fully weighted undirected correlation matrices by calculating a zero-leg Pearson's correlation coefficients between each pair of regions, which was followed by the assessment of community-based network structure based on segregation and clustering of functional within-network communities. Compared to HV, all patients showed extensive bilateral decreases within the sensorimotor networks (SMN), including the primary sensorimotor, premotor, inferior parietal, superior/middle temporal cortices and supplementary motor area, and within the frontoparietal network (FPN), including the left prefrontal cortex and bilateral middle temporal gyrus. Direct comparisons between TSD and NTSD showed SMN differences in the bilateral primary somatosensory cortex in NTSD and the right sensorimotor cortex in TSD, while FPN differences were found in the inferior parietal cortex in TSD only. Graph analysis showed differences in nodal participation in five neural communities in patients vs. HV, which led to either expansion or reduction of these communities with subsequent reconfiguration of global network topology in TSD and NTSD. Compared to HV, NTSD had significantly increased nodal

degree and decreased nodal strength, whereas TSD had abnormal formation of hubs in the left insula and bilateral temporal cortex. Our results indicate that focal dystonias are network disorders, which are characterized by greater cortical involvement in TSD possibly attributed to a finer sensorimotor control of highly learned human behaviors, such as writing and speaking.

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Poster

583. Dystonia and Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 583.21/D47

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Tyler's Hope for a Dystonia Cure, Inc.

Dystonia Medical Research Foundation

Bachmann-Strauss Dystonia and Parkinson Foundation, Inc.

NIH Grant NS37409, NS47466, NS47692, NS54246, NS57098, NS65273, NS72782, NS74423 and NS82244

Title: Altered dopamine receptor 1-positive medium spiny neuron activity and impaired motor-skill transfer in Dyt1 ΔGAG heterozygous knock-in mice

Authors: *F. YOKOI[1], H. CHEN[1], M. T. DANG[3], J. LIU[4], J. R. GANDRE[1], K. KWON[1], R. YUEN[5], S. N. ROPER[2], Y. LI[1];
[1]Neurol., [2]Neurosurg., Univ. of Florida, Gainesville, FL; [3]Children's Hosp. of Philadelphia, Philadelphia, PA; [4]Ctr. for Neurodegeneration and Exptl. Therapeutics, Neurol., Univ. of Alabama at Birmingham, Birmingham, AL; [5]Radiology, St. Louis Univ., Saint Louis, MO

Abstract: DYT1 dystonia is a movement disorder caused by a trinucleotide deletion (ΔGAG) in DYT1 (TOR1A), corresponding to a glutamic acid loss in the C-terminal region of torsinA. Functional alterations in the basal ganglia circuits have been reported in both DYT1 dystonia patients and rodent models. However, the role of the direct pathway in the pathogenesis is not yet clear. Here, the direct pathway was analyzed in Dyt1ΔGAG heterozygous knock-in (KI) mice. Since the contribution of the direct pathway to motor-skill learning has been suggested in another pharmacological rat model injected with a dopamine receptor 1 (D1R) antagonist, we developed

a novel motor-skill transfer test and analyzed the performance in Dyt1 KI mice. Methods; D1R binding assay: The striatal homogenates were incubated with [3H]SCH-23390, filtered through glass filters and measured by a liquid scintillation counter. D1R autoradiography: The coronal brain sections were incubated with [3H] SCH-23390 and exposed to an imaging plate. Western blot: The striatal D1R and other membrane protein levels were measured by either fluorescence or chemiluminescence systems. Quantitative real-time RT-PCR: The relative quantities of the striatal D1R mRNA were analyzed with SYBR. Immunohistochemistry: The striatal D1 neurons were stained in the coronal sections and counted. Electrophysiology: The miniature excitatory postsynaptic currents (mEPSCs) were recorded with TTX on direct pathway EGPF-labeled medium spiny neurons in the brain slices by a whole-cell voltage-clamp. Motor-skill transfer test: Mice in treated group were trained for two weeks on a treadmill for 5 minutes each day. Two days after the training, all mice were tested on a rotarod for three trials in one day. The control was untrained mice. Results and Conclusions; Dyt1 KI mice exhibit decreased striatal D1R binding activity and D1R protein levels, suggesting an alteration of the direct pathway. The decreased D1R may be caused by translational or post-translational processes since Dyt1 KI mice had normal levels of striatal D1R mRNA and a normal number of striatal D1 neurons. The levels of striatal ionotropic glutamate receptor subunits, dopamine transporter, acetylcholine muscarinic M4 receptor and adenosine A2A receptor were not altered suggesting a specificity of affected polytopic membrane-associated proteins. Dyt1 KI mice also exhibited altered mEPSCs, suggesting a functional alteration of the direct pathway. Consistent with the D1 antagonist model, Dyt1 KI mice showed motor skill transfer deficits. Further characterization of both the direct and the indirect pathways in Dyt1 KI mice will aid the development of novel therapeutic drugs.

Disclosures: **F. Yokoi:** None. **H. Chen:** None. **M.T. Dang:** None. **J. Liu:** None. **J.R. Gandre:** None. **K. Kwon:** None. **R. Yuen:** None. **S.N. Roper:** None. **Y. Li:** None.

Poster

583. Dystonia and Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 583.22/D48

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Title: Role of the Na+ leak current channel in involuntary movement disorders in *C. elegans*

Authors: *M. KASAP[1], E. AAMODT[2], D. DWYER[3];
[1]Pharmacology, Toxicology and Neurosci., [2]Biochem. and Mol. Biol., [3]Psychiatry, LSU Hlth. Sci. Ctr. Shreveport, Shreveport, LA

Abstract: The human sodium leak current channel (NALCN) is implicated in many genetic forms of the movement disorders such as dystonia and dyskinesia. Mutations in NALCN cause similar abnormalities in mice, *Drosophila* and *C. elegans*. Reduced NALCN expression in *Drosophila* altered locomotive behavior and circadian rhythms although the flies were viable and fertile. Also, they displayed a narrow abdomen phenotype with 'hesitant walking' and had altered sensitivities to general anesthetics such as halothane. Loss-of-function mutation in *C. elegans* NALCN caused animals to move extremely slowly and when touched on the tail they showed a fainting or freezing response similar to frozen gait in Parkinson's disease patients. Gain-of-function mutation in NALCN caused an extremely active phenotype; worms showed excess coiling, turns and reversals similar to dystonia and dyskinesia. We think that mutations in NACLN disrupt the depolarization-repolarization balance by changing the relative concentrations of sodium, calcium and potassium inside the cell. Previously, we showed that it is possible to correct movement of NALCN loss-of-function animals with nicotine and K^+ channel blockers. Therefore, we hypothesized that we should be able to correct movement in gain-of-function (*gf*) mutant animals [*unc-77* (*e625*) allele] with a similar strategy. In order to evaluate the movements of the worms, we observed spontaneous movement, startle response and foraging (food seeking) behavior. Our studies with potassium channel activators on *gf* animals remain inconclusive except 2-aminoethoxydiphenyl borate (2-APB). 2-APB is a pharmacological agent with various actions such as such as inhibiting inositol trisphosphate receptors, transient receptor potential channels, and gap junctions; and modifying store-operated calcium channels function. Beside 2-APB, we discovered several pharmacological agents such as nimodipine, flunarizine and ethoxzolamide that improve or correct the movement of *gf* animals in the foraging assay. These drugs potentially share a common mechanism of action by regulating calcium flux. We hope to discover specific pharmacological agents that target the NALCN. Drugs that can correct behavioral deficits caused by NALCN mutations may be useful for the treatment of human movement disorders.

Disclosures: M. Kasap: None. **E. Aamodt:** None. **D. Dwyer:** None.

Poster

583. Dystonia and Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 583.23/E1

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Brian Jackson Dystonia Research and Discovery Fund

Title: BDNF and NMDA receptor expression in X-linked dystonia Parkinsonism neural stem cells

Authors: *L. ZHANG[1], D. M. MCCARTHY[2], T. J. MORGAN, Jr[2], K. SHIN[3], W. T. HENDRIKS[3], D. C. BRAGG[3], P. G. BHIDE[2];
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Abstract: X-linked dystonia Parkinsonism (XDP) is characterized by progressive torsion dystonia accompanied with or followed by Parkinsonism. The mechanisms of XDP pathogenesis are poorly understood. However, selective loss of striatal patch neurons, likely due to excitotoxic injury, is believed to be a major contributor. We reprogrammed fibroblasts from XDP patients and neurologically normal (control) family members. Genotyping confirmed that the XDP patients contained all known XDP haplotype markers, whereas the controls did not. Pluripotent cells were converted to neural stem cells (NSCs), which exhibited characteristic NSC morphology and molecular markers. NSCs were examined for protein expression by western blot. Both XDP and control NSCs expressed the BDNF receptor TrkB. Control NSCs did not express either of the two NMDA receptor subunits examined, namely subunit 1 or 2B. However, the XDP NSCs expressed subunit 2B but not 1. Since NMDA receptors 1 and 2 mediate excitotoxicity, we exposed control NSCs to NMDA directly and assayed excitotoxicity by LDH release. NMDA (25, 50 or 250 μM) exposure even for 12 hr did not produce excitotoxicity confirming the absence of the NMDA receptors in control NSCs. The expression of NMDA receptors in the XDP patient derived NSCs suggests increased vulnerability of the cells to NMDA excitotoxicity supporting the notion that excitotoxic injury is associated with XDP neuropathology. Since the XDP patient derived NSCs also express TrkB receptors, and since BDNF is known to be protective against NMDA-induced neurotoxicity, we are examining whether exogenous BDNF can protect XDP patient derived NSCs from NMDA induced excitotoxicity. Collectively, our data promise novel insights into mechanisms of XDP neuropathology and a protective role for BDNF.

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Poster

583. Dystonia and Parkinson's Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 583.24/E2

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: Brian Jackson Dystonia Research and Discovery Fund

Parkinson's and Movement Disorders Foundation (PMDF)

Florida Translational Research Program

Title: Overriding upstream reading frames associated with L-dopa responsive dystonia and other human diseases

Authors: *L. JONES, E. DAVILA, L. K. GOODE, P. G. BHIDE, I. ARMATA;
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Abstract: Within the human genome, approximately 28% of genes contain at least one functional upstream translation start codon (uATG). Translation initiation at a functional uATG can result in a uATG-initiated peptide and competitively prevent the initiation of translation at the canonical start codon (cATG) and production of the physiological cATG-protein. The competition between the uATG and cATG functions as a regulatory mechanism to control and maintain optimal levels of the cATG-protein. The remaining 72% of the human genes are devoid of uATGs and optimal translation levels are solely achieved by the presence of the cATG. A variety of human diseases are the result of single nucleotide polymorphisms (SNPs) that introduce one or more novel uATG in the upstream region of genes (72%). As a result, the competition arising from the uATG leads to downregulation or even abolishment of the cATG-translated protein. Such SNPs have been linked with manifestation of cancer, thrombotic predisposition, cleft lip syndrome, β-thalassemia and other serious human diseases. We have uncovered a -22C>T SNP within the upstream region of the GCH1 gene that introduces a functional uATG. The GCH1 gene normally lacks uATGs. Introduction of this -22C>T uATG leads to translation of a short, mutant peptide with a distinct amino-acid sequence and function compared to the physiological cATG-translated protein. The uATG competes with the cATG and nearly eliminates the GCH1 protein leading to manifestation of dopa-responsive dystonia. Presently, there is no treatment for diseases associated with uATGs. We used the GCH1-uATG/cATG as a model to develop sensitive high-throughput screening (HTS) to identify compounds that promote read-through of the uATG allowing initiation of translation on the normal cATG. Compounds that tilt the balance toward the cATG promoter will result in restoration of normal cATG-translation levels and thus, can serve as potential therapeutic agents for the whole group of uATG-related diseases.

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Poster

583. Dystonia and Parkinson's Disease

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Program#/Poster#: 583.25/E3

Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH Grant EY022358

Title: Cytoskeletal and mitochondrial-related protein changes within the DBA/2J visual projection

Authors: *G. N. WILSON[1,2], D. M. INMAN[2], S. D. CRISH[2];
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Abstract: Cytoskeletal changes and deficits in axonal transport are among the earliest hallmarks of many neurodegenerative diseases, including glaucoma. Addressing these pre- and early degenerative changes in abnormal protein accumulation and cytoskeletal modifications may provide the best opportunity for treating these disorders prior to functional loss. Microtubules provide the substrate upon which molecular motors travel while transporting cargo along the axon. Organization of this microtubule matrix is mediated by the microtubule-associated protein tau. Site specific phosphorylation of tau has received special attention for its role in neurodegenerative disorders like Alzheimer's disease. Using magnetic bead multiplexing, enzyme-linked immunosorbent assays, and immunofluorescence we found early elevations in total tau and phospho-tau (ptau231) within the optic nerve of pre-glaucomatous DBA/2J mice followed by an age-dependent decrease. Interestingly, ptau231 and total tau were significantly elevated in retina of older DBA/2J mice, suggesting a translocation of phosphorylated tau from axons into somatodendritic compartments. Also using protein multiplex assays, we quantified levels of Park5 (Uchl1) and Park7 (DJ-1) in retina and optic nerve of pre-glaucomatous, early, and late glaucomatous DBA/2J mice and found pre-glaucomatous elevations in the optic nerve, while not observing elevations in the retina until animals reached late glaucomatous ages. Both of these proteins have been shown to play a role in neurodegeneration and to play a potential role in protein kinase regulation, involved in post-translational modification of cytoskeletal elements. Park 7 is involved in mitochondrial quality control and has been shown specifically to affect extracellular signal-regulated kinase (ERK). As predicted, activated ERK1/2 levels within the retina were elevated in the same DBA/2J age groups; we also observed that phosphorylation of ERK peaked at early glaucomatous ages (8-10 months) in both retina and optic nerve. Phosphorylated ERK levels remained significantly elevated in the retina even at ages representing late glaucomatous pathology (12-15 months). Understanding how these cytoskeletal

and mitochondrial-related protein changes impact the progression of glaucoma may present new therapeutic avenues for this debilitating disease.

Disclosures: **G.N. Wilson:** None. **D.M. Inman:** None. **S.D. Crish:** None.

Poster

584. Autism: Synaptic and Cellular Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 584.01/E4

Topic: C.06. Developmental Disorders

Support: Alberta Children's Hospital Foundation

Alberta Children's Hospital Research Institute for Child and Maternal Health

Title: Alterations in complex ii of the electron transport chain are associated with elevated mitochondrial respiration in btbr mouse model of autism spectrum disorder

Authors: ***Y. AHN**, R. MYCHASIUK, N. CHENG, N. C. YEE, R. TOBIAS, J. M. RHO; Pediatrics, Alberta Children'S Hosp. Res. Inst., Calgary, AB, Canada

Abstract: Autism spectrum disorder (ASD) is a highly prevalent neurodevelopmental condition that is characterized by specific behavioral and cognitive impairments, and is believed to arise from heterogeneous causes. Although a single and unifying pathophysiological mechanism is unlikely, there is growing evidence that mitochondrial dysfunction may play a critical role in provoking behavioral symptoms. Here, we hypothesized that impaired mitochondrial bioenergetics may be a contributing factor in ASD pathogenesis. To demonstrate this, we examined mitochondrial functional parameters in acutely isolated mitochondria from the frontal and lateral temporal neocortices of BTBR mice which have been widely studied and validated as a clinically relevant murine model of ASD. Specifically, for each BTBR or control (C57) animal, we measured the mitochondrial oxygen consumption rate (OCR) using a Seahorse Bioscience XF24 analyzer, and also determined ATP levels and ROS production using standardized assay kits. We observed significantly higher OCR levels in BTBR mice ($p<0.001$, N=7/group). Further, compared to control animals, we found that ATP levels were increased in BTBR mice (1.10±0.13 vs. 1.90±0.18; $p<0.001$; N=12/group) and ROS production was decreased in BRBR mice (1700±130 vs. 1100±180; $p<0.05$; N=4/group). To determine an underlying mechanism for the observed higher mitochondrial respiration in BTBR mice, we measured mitochondrial oxidative phosphorylation (OXPHOS) protein levels using western blot assays. Among the 5

complexes in the electron transport chain (ETC), Complex II expression was significantly increased in BTBR mice (1.000±0.005 vs. 1.300±0.056; $p<0.001$, N=8/group). As complex II is composed of 4 subunits (SDHA, SDHB, SDHC, and SDHD), we quantified their relative gene expression in frontal and temporal cortices using RT-qPCR. Sdha was decreased in BTBR mice, but this was not significant. Expression levels of Sdhb, Sdhc, and Sdhd were also increased in BTBR mice ($p=0.15$ for Sdhb; $p=0.054$ for Sdhc; $p=0.029$ for Sdhd, N=6/group). Furthermore, the activity of the Complex II enzyme, succinate dehydrogenase (SDH), was significantly higher in autistic mice than C57 controls ($p<0.001$, N=6/group). Collectively, these observations suggest that the dysregulation of the mitochondrial respiratory function, especially abnormalities of Complex II in brain may be an important contributor to the autistic phenotype of BTBR mice, and provide further evidence that abnormalities in mitochondrial function may underlie in part the behavioral features of ASD.

Disclosures: **Y. Ahn:** None. **R. Mychasiuk:** None. **N. Cheng:** None. **N.C. Yee:** None. **R. Tobias:** None. **J.M. Rho:** None.

Poster

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Topic: C.06. Developmental Disorders

Support: NIH Grant 1 R01 AG048131-01

Title: Modeling Shankopathies in genetically edited human induced neurons

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Abstract: The clinical and genetic landscapes of human neurological disorders are often highly heterogeneous thereby molecular mechanisms behind them remain largely elusive. As the most profound member of the Shank gene family, Shank3 is an important synaptic protein enriched in the postsynaptic density (PSD) of excitatory glutamatergic synapses where it scaffolds an extensively complex protein density. It is one of the most promising candidate genes for autism spectrum disorders (ASD) and intellectual disability (ID), as well as considered primarily responsible for clinical manifestations of the Phelan-McDermid syndrome (PMS; 22q13.3 deletion syndrome). Enormous previous efforts have been spent to study the Shank3 deficiency in neuronal diseases using mouse genetic models or human induced pluripotent stem cells

(iPSC). However, major neuronal or behavior manifestations observed from those models were incongruent, which further adds to the elusivity of the functional involvement of Shank3 in disease development. Besides, innate limitations of mouse models in studying human neurological disorders and the fact that a direct proof of functional role of Shank3 in human neurons was negligible due to the inaccessibility of human neurons harboring Shank3 mutation in a clean genetic background are major obstacles in studying Shank3 in human neurological diseases. In this regard, here we report the generation of conditional Shank3 knockout human neurons based on gene editing in human embryonic stem cells (ESC). Induced neurons (iN) differentiated from human ESC conditionally deficient in Shank3 revealed neuronal morphological and synaptic deficits when closely compared to their conditional control counterparts. Our model recapitulated major defects in neuronal morphology and synaptic transmission observed in previous Shank3 mouse or human PMS iPSC models; moreover, our model revealed an unappreciated role of Shank3 in affecting intrinsic neuronal properties. Indeed, our conditional gene knockout approach renders us significant advantages over previous models in investigating the authentic functional readouts of Shank3 deficiency in human neurons with clean genetic background. Novel discoveries of intrinsic electrophysiological property defects caused by Shank3 haploinsufficiency in human neurons will be presented.

Disclosures: **F. Yi:** None. **T. Danko:** None. **T. Sudhof:** None.

Poster

584. Autism: Synaptic and Cellular Mechanisms I

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Topic: C.06. Developmental Disorders

Support: Helmholtz Gesellschaft VH-VI-510

European Unions Seventh Framework Programme (FP7/2007-2013)

Title: Characterization of ASD-associated Shank proteins in early development of rat hippocampal neurons

Authors: *S. C. HALBEDL, M. SCHOEN, T. BOECKERS, M. SCHMEISSER;
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Abstract: Shank1, Shank2 and Shank3 are essential scaffold proteins of the postsynaptic density (PSD) of excitatory glutamatergic synapses. In the PSD, Shank proteins multimerize and build

large molecular platforms thus providing multiple protein-protein-interaction sites, thereby linking postsynaptic receptors with their downstream signaling proteins and the actin cytoskeleton of dendritic spines. Over the last decade, mutations in those genes were found to play a central role in the pathogenesis of neuropsychiatric disease, predominantly autism spectrum disorders (ASD). Interestingly, two studies have already implicated a role of Shanks in early development of primary hippocampal neurons by revealing Shank2 and Shank3 immunoreactivity in growth cones (Du et al., 1998; Durand et al., 2012). For a more detailed analysis of Shanks in early neuronal development, we started to examine rat hippocampal neurons at distinct early developmental stages (DIV1, DIV2, DIV3, DIV4 and DIV7) before synaptogenesis takes place. So far we could show that all Shanks are indeed found in early rat hippocampal neurons and that they exhibit interesting expression dynamics and subcellular localizations over time, strongly supporting a novel role in early neuronal development compared to their well-known function during the formation of postsynaptic specializations. We are now using different *in vitro* and *in vivo* model systems to elucidate the role of these proteins in early neuronal differentiation and will present interestingly new results on the poster.

Disclosures: **S.C. Halbedl:** None. **M. Schoen:** None. **T. Boeckers:** None. **M. Schmeisser:** None.

Poster

584. Autism: Synaptic and Cellular Mechanisms I

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Topic: C.06. Developmental Disorders

Support: SFARI Explorer Award

NARSAD Independent Investigator Award

Title: Novel signaling and neurodevelopmental mechanisms in a mouse model of psychiatric pathogenesis

Authors: *R. E. STANLEY, P. M. MARTIN, A. E. FREITAS, A. P. ROSS, B. N. R. CHEYETTE;
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Abstract: The Wnt/β-catenin signaling pathway is broadly involved in neural development and is considered a potential pathogenic neurodevelopmental pathway in psychiatric illness. DISC1,

mutations in which confer susceptibility to schizophrenia as well as to other major psychiatric disorders, regulates this pathway in developing neurons. GSK3, the central kinase in this pathway, is a pharmacological target of the mood-stabilizing agent lithium. Recent human genetic studies have increased interest in Wnt signaling by finding that mutations in several components of the pathway confer genetic susceptibility to autism spectrum disorders (ASD). We have been investigating neurodevelopmental and behavioral functions of DIXDC1, a DISC1-interacting protein that also regulates Wnt/β-catenin signaling during neural development. We have generated a Dixdc1 knock-out mouse and performed neurodevelopmental, behavioral, and pharmacological studies in these animals, combined with human genetic analyses focused on the DIXDC1 locus, and rescue and gain-of-function experiments involving human alleles of Dixdc1. Mice homozygous for loss-of-function of Dixdc1 are viable and appear normal. We have found that loss of Dixdc1 leads to dose-sensitive deficits in behavioral assays thought to model depression and social behavior. These deficits are responsive to correction by acute administration of lithium or a small-molecule GSK3-inhibitor. Forebrain pyramidal neurons from Dixdc1 knock-out animals have normal dendritic arborization but reduced dendritic spines and glutamatergic synapses. These phenotypes can be rescued by expression of a wild type human DIXDC1 cDNA, but not by some rare alleles found in ASD patients. Moreover, a subset of these rare alleles with aberrant Wnt/β-catenin signaling activity have dominant-negative effects in neurodevelopmental assays. Our data support a role for Dixdc1 in the generation of excitatory synapses in the forebrain and suggest that this occurs downstream of activity in the Wnt/β-catenin signaling pathway within differentiating pyramidal neurons. Moreover, our data suggest that this is highly sensitive to DIXDC1 allelic dosage and to rare missense alleles at this locus, with effects on complex behaviors in animal models relevant to psychiatric pathology.

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Poster

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Topic: C.06. Developmental Disorders

Support: Lurie Center for Autism

Title: Effects of maternal immunoactivation on neurotransmission in mpfc-amygdala circuits

Authors: Y. LI[1], B. C. FINGER[1], S. M. LANDINO[1], C. J. MCDOUGLE[2], W. A. CARLEZON, Jr.[1], *V. Y. BOLSHAKOV[1];
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Abstract: Both the medial prefrontal cortex (mPFC) and the amygdala have been repeatedly implicated in the etiology of autism-spectrum disorders (ASD). Presently, there is significant evidence that autism is the neural network phenomenon which may reflect dysregulation of functional interactions between certain regions of the brain, including the mPFC and the amygdala. The amygdala receives strong projections from the mPFC and contributes to regulation of social behaviors. As the deficit in social behaviors is one of the hallmarks of autism, it is possible that the functional connectivity between the mPFC and amygdala may be affected during the development of ASD. We explored this possibility by assaying the effects of Poly I:C-triggered maternal immunoactivation (MIA), an animal model of ASD, on neurotransmission in projections from the mPFC to the basolateral nucleus of the amygdala (BLA) in the offspring of immunoactivated female mice. The BLA was targeted in the course of these recordings because it is most densely innervated by prefrontal fibers. Using optogenetic techniques, we found that MIA was associated with increased synaptic strength in glutamatergic projections from the mPFC to neurons in the BLA without affecting functional expression of channelrhodopsin. Potentiation of synaptic responses was not accompanied by changes in the paired-pulse ratio, suggesting a postsynaptic expression mechanism. In contrast, the magnitude of GABAergic inhibitory postsynaptic responses resulting from activation of local circuit interneurons in the BLA by prefrontal fibers was diminished in the offspring of immunoactivated mice. Therefore, the balance between excitation and inhibition in mPFC-BLA projections was shifted toward a greater functional efficiency of excitation. The latter, resulting in the enhanced probability of neuronal firing in the BLA in response to incoming afferent signals arising from the mPFC, could potentially contribute to autistic-like behavioral modifications in the offspring of immunoactivated mice.

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Poster

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Topic: C.06. Developmental Disorders

Support: DOD/CDMRP Autism Research Program Idea Development Grant

Nebraska Research Initiative

DHHS/NIH P20RR018788

Title: Impaired synaptic development in a maternal immune activation mouse model of neurodevelopmental disorders

Authors: P. COIRO[1], P. RAGUNATHAN[1], A. SURESH[1], E. SPARTZ[1], G. PENDYALA[1], S. CHOU[2], Y. JUNG[1], B. MEAYS[1], S. ROY[1], M. LI[2], *A. DUNAEVSKY[1];
[1]Developmental Neurosci., Univ. of Nebraska Med. Ctr., Omaha, NE; [2]Dept. of Psychology, Univ. of Nebraska –Lincoln, Lincoln, NE

Abstract: Both genetic and environmental factors are thought to contribute to neurodevelopmental disorders with maternal immune activation (MIA) being a risk factor for both autism spectrum disorders and schizophrenia. Here, using different cellular and molecular approaches with electrophysiological and behavioral analysis, we have investigated synaptic structure in the somatosensory cortex of MIA mouse model. Using *in vivo* multiphoton imaging, we determined that there is reduction in number and turnover rates of dendritic spines, sites of excitatory synaptic contacts in the cortex of young MIA offspring. The spine impairments, confirmed by confocal analysis, persisted into adulthood and correlated with increased repetitive behavior, an ASD relevant behavioral phenotype. Analysis of synaptic inputs revealed an increase in proportion of dendritic spines that were contacted by both excitatory and inhibitory presynaptic terminals (VGluT1and GAD) and these structural impairments were accompanied by altered excitatory and inhibitory synaptic transmission. Furthermore, we have confirmed that MIA results in increase in the surface expression of the major histocompatibility complex I (sMHCI) proteins in brain slices. Finally, a postnatal treatment of MIA offspring with the anti-inflammatory drug, ibudilast, prevented both synaptic and behavioral impairments. Our results suggest that altered inflammatory state associated with maternal immune activation results in increased level of sMHCI and in impaired synaptic development persisting into adulthood but which can be prevented with early anti-inflammatory treatment.

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Poster

584. Autism: Synaptic and Cellular Mechanisms I

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Topic: C.06. Developmental Disorders

Support: JSPS KAKENHI 26460094

JSPS KAKENHI 26117504

Title: Dysfunction of microglia-mediated reorganization of dentate gyrus-CA3 circuits in a mouse autism model

Authors: *K. SHIBATA, R. KOYAMA, K. MORISHITA, Y. IKEGAYA;
Lab. Chem. Pharmacol., Grad. Sch. Pharmaceut. Sci., Univ. Tokyo, Tokyo, Japan

Abstract: Selective pruning of inappropriate synapses by microglia is fundamental to the development of functional neural circuits. Increasing evidence suggests that one of the earliest events in autism spectrum disorders (ASDs) is the deficits in a balance between excitatory and inhibitory synapses; however, whether and how microglia-mediated synapse elimination is involved in synaptic dysfunction in ASDs remains unknown. We report that microglia-mediated synapse elimination was attenuated in the hippocampus of mouse offspring from mothers that experienced maternal immune activation (MIA), which is known as a risk factor for ASDs in offspring. In control mice, the dentate gyrus-CA3 synaptic connections were refined through activity- and microglia-dependent elimination of the mossy fiber synapses through postnatal 2 to 4 weeks old. In contrast, the elimination of mossy fiber synapses by microglia was attenuated in mice whose mothers experienced MIA during pregnancy. Importantly, the excess synapses were detected as early as postnatal 4 weeks old and maintained throughout adulthood. Finally, voluntary wheel running from postnatal 4 to 8 weeks old enhanced microglia-mediated engulfment of the mossy fiber synapses in MIA groups and successfully decreased the synapse density to control levels. This process was also mediated by microglia. Thus, our finding suggests that the early-life deficits in microglia-mediated synapse elimination take place in ASD hippocampus and that exercise in adolescence may prevent MIA-dependent synaptic imbalance in ASDs.

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Poster

584. Autism: Synaptic and Cellular Mechanisms I

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Topic: C.06. Developmental Disorders

Support: Wellcome Trust

Tuberous Sclerosis Association

The Patrick Wild Centre

Title: Identifying translating mRNAs involved in pathological synaptic plasticity

Authors: *S. R. THOMSON[1], M. F. BEAR[2], E. K. OSTERWEIL[1,2];
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Abstract: Fragile X syndrome (FXS) and Tuberous Sclerosis Complex (TSC) are single-gene syndromic disorders that share a high incidence of autism spectrum disorder and intellectual disability (ASD/ID). Because they are genetically defined and can be effectively modelled in animals, the study of these disorders has been valuable in understanding the molecular mechanisms of ASD/ID. Both FXS and TSC are caused by mutation of genes that function in mRNA translation. In the *Fmr1*$^{-/y}$ mouse model, basal protein synthesis is excessive and there is an exaggeration of long-term depression (LTD) induced by Gp1 metabotropic glutamate receptor (mGluR) activation in hippocampal CA1. In the *Tsc2*$^{+/-}$ mouse, hippocampal protein synthesis and mGluR-LTD are deficient. Mice bred to carry both *Fmr1*$^{-/y}$ and *Tsc2*$^{+/-}$ mutations display normal protein synthesis rates and mGluR-LTD. Thus, FXS and TSC mouse models exhibit mirror alterations in the same cellular process, synaptic protein synthesis, suggesting a point of convergence for multiple genetic causes of ASD/ID. The identity of the mRNAs translated to support mGluR-LTD, and mis-translated at *Fmr1*$^{-/y}$ and *Tsc2*$^{+/-}$ synapses, is not known. We are addressing this question using Translating Ribosome Affinity Purification (TRAP) to isolate mRNAs specifically translated in CA1 pyramidal neurons and dendrites of *Fmr1*$^{-/y}$, *Tsc2*$^{+/-}$, and *Fmr1*$^{-/y}$x*Tsc2*$^{+/-}$ mutant mice. Using this approach, we can compare the translatomes of WT versus mutant neurons, under both control and LTD conditions. Our preliminary experiments show a consistent isolation of CA1 pyramidal cell-specific translating mRNAs from whole hippocampus or from acute hippocampal slices. We are identifying these mRNAs in WT and mutant samples using next-generation RNA sequencing, and performing follow up studies to assess the role of identified targets in plasticity and the pathogenesis of ASD/ID. Unexpectedly, our preliminary results show that mRNA encoding the GluA2 subunit of the AMPA-type glutamate receptor (AMPAR) is overrepresented in *Fmr1*$^{-/y}$ ribosomes in CA1 pyramidal neurons. Metabolic labeling experiments confirm that GluA2 is over-translated in *Fmr1*$^{-/y}$ hippocampal slices. We are currently investigating the role of this change in the pathological phenotypes observed in the *Fmr1*$^{-/y}$ hippocampus.

Disclosures: **S.R. Thomson:** None. **M.F. Bear:** None. **E.K. Osterweil:** None.

Poster

584. Autism: Synaptic and Cellular Mechanisms I

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Title: Tsc2-deficiency induced mTOR hyperactivity impairs spatiotemporal dynamics of mitophagy in neurons

Authors: *D. EBRAHIMI-FAKHARI[1,3], A. SAFFARI[3], L. WAHLSTER[2], A. DINARDO[1], M.-J. HAN[1], M. SAHIN[1];
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Abstract: Objectives: Tuberous sclerosis complex (TSC) is a neurodevelopmental disorder caused by mutations in *TSC1* or *TSC2,* which encode critical regulators of mTORC1. Loss of *TSC1* or *TSC2* renders an mTOR hyperactive state resulting in abnormal neuronal metabolism and impaired autophagy. Whether this leads to deficits in mitochondrial trafficking or mitochondrial degradation by autophagy (mitophagy) is unknown. Using TSC as a genetically tractable model, the objective of this study is to determine whether mTOR hyperactivity alters the spatiotemporal dynamics of mitochondrial transport and mitophagy in neurons. **Methods:** To study mitochondrial turnover, we use a combination of gene knockdown, pharmacology, live imaging probes, time lapse confocal microscopy, immunocytochemistry and biochemical assays in cultured embryonic rat neurons and cortical neurons differentiated from induced pluripotent

stem cells (iPSC) of TSC patients and controls. **Results:** Knockdown of *Tsc2* in neurons leads to uncoordinated axonal transport of mitochondria, which is reversed by treatment with the mTORC1-inhibitor rapamycin. Following acute loss of mitochondrial membrane potential ($_m\Psi$), depolarized mitochondria are rendered stationary with a subset showing enhanced retrograde transport in control neurons. No such retrograde transport pattern is found in *Tsc2*-deficient neurons, pointing to impaired translocation and clearance of damaged mitochondria from axons. The presence of mitochondria with reduced $_m\Psi$ in neurites is confirmed in iPSC-derived cortical neurons from TSC patients. Examining the spatiotemporal dynamics of mitophagy, we find that *Tsc2*-deficient neurons show enhanced Parkin-translocation to mitochondria at baseline. Large p62-positive aggregates and enlarged LC3-positive autophagic vesicles accumulate, suggesting reduced turnover through autophagy. Probing the recruitment of the autophagy machinery following induction of mitophagy, we find impaired formation and turnover of autophagosomes in *Tsc2*-deficient neurons. Impaired autophagosome-lysosome fusion is quantified using a GFP-mCherry-LC3 tandem assay. Mitochondria-targeted mKeima is employed to quantify mitophagy. **Conclusions:** TSC provides a genetically tractable model to examine the impact of hyperactive mTOR signaling on mitochondrial transport and turnover. Specific deficits in axonal and global mitophagy are present in *Tsc2*-deficient neurons. Accumulation of damaged mitochondria in axons could lead to impaired synaptic signaling and thus may contribute to complex disease manifestations such as autism-spectrum disorder or intellectual disability.

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Poster

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Topic: C.06. Developmental Disorders

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NSERC

Title: Examining the role of dixdc1 in neural connectivity and autism spectrum disorder

Authors: *V. KWAN[1], C. HUNG[1], N. HOLZAPFEL[1], K. HABING[1], N. MURTAZA[1], S. WALKER[2], S. SCHERER[2], K. HOPE[1], R. TRUANT[1], K. SINGH[1];
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Abstract: Emerging studies suggest that molecules in the Wnt signalling pathway are important for the development of neural connectivity and are associated with autism spectrum disorders (ASDs). We are studying a Wnt signalling molecule named DIX domain containing-1 (DIXDC1), a homolog of Disheveled and Axin that has previously been linked to psychiatric disorders. Preliminary results, using mouse *in vitro* and *in vivo* models, show that decreasing the expression of DIXDC1 reduces dendrite outgrowth, and dendritic spine formation and maturation. Additionally, we found that DIXDC1 may function through an actin-dependent mechanism to regulate actin dynamics and polymerization. We also found that phosphorylation of DIXDC1 mediates dendritic spine formation through modulation of actin dynamics. Finally, using exome sequencing of families with ASDs, we discovered rare inherited genetic variants in DIXDC1. Expression of these variants in primary neurons causes impaired dendrite and dendritic spine development. Future work being conducted will reveal the role of DIXDC1 in neurodevelopment using electrophysiological approaches to determine its impact on neuronal function and ASDs. Together these data suggest a novel DIXDC1 pathway for synaptic development and its possible role in neural connectivity defects associated with ASDs.

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Poster

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Support: 5R01 MH081754

5R01 MH100027

3P50 HD055784

5P30HD004612

Title: Synaptic alterations in the striatum and the cortex of a new mouse model of autism spectrum disorders: JAKMIP1 knock-out mouse

Authors: *L. GALVAN[1], J. BERG[2], J. Y. CHEN[1], C. CEPEDA[1], D. GESCHWIND[2], M. S. LEVINE[1];
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Abstract: Autism spectrum disorders (ASD) are developmental conditions characterized by alterations in social interaction, communication and behavior. Major effect mutations such as the inherited duplication of 15q11-q13 (dup(15q)) or FMR1 gene (Fragile X mental retardation), are associated with ASD. Mutations in the FMR1 gene lead to the loss of FMR protein, a translational repressor. Its absence disturbs synaptic plasticity and neuronal development. Animal models of Fragile X syndrome do not display a robust behavioral phenotype. Interestingly, previous studies analyzing the transcriptome of lymphoblastoid cells from autistic males diagnosed with ASD and Fragile X syndrome, ASD and dup(15q), and idiopathic ASD revealed that all patient groups had altered levels of janus kinase and microtubule-interacting protein 1 (JAKMIP1). The present study examined electrophysiological alterations in a recently generated JAKMIP1 knock-out (KO) mouse. These animals displayed a striking stereotypical behavioral phenotype consisting of "jumping." This motor stereotypy suggested a potential involvement of basal ganglia circuits. We investigated whether the striatum could contribute to the development of the phenotype in these animals. We recorded medium-sized spiny neurons (MSNs) in the dorsal striatum of male juvenile (P14) and male adult (2-3 months) JAKMIP1 KO and wildtype (WT) littermate mice using whole-cell patch clamp recordings in voltage clamp mode. Cortical pyramidal neurons (CPNs) in layer II/III also were recorded in adult KO and WT mice. In the striatum, adult JAKMIP1 KO mice displayed a significant increase in frequency of spontaneous inhibitory (IPSCs) and excitatory postsynaptic currents (EPSCs) suggesting up-regulation of GABA and glutamate neurotransmission in MSNs. In the cortex, adult JAKMIP1 KO mice also showed an increase in spontaneous EPSC frequency but did not display changes in IPSCs. To examine glutamate receptor-mediated responses in MSNs we used electrical stimulation to evoke AMPA receptor (AMPAR)- and NMDA receptor (NMDAR)-mediated currents. The amplitude of the AMPAR response was not altered at both ages. In contrast, the charge and the decay time of the NMDAR response were significantly increased in the P14 but not in the 2-3 month KO mice. Interestingly, a proportion of KO MSNs showing an AMPAR response failed to display a NMDAR response at both ages. These results demonstrate that there are significant alterations in synaptic activity in the cortex and striatum of JAKMIP1 KO mice. Future studies will be aimed an uncovering the cellular mechanisms for these changes in neuronal communication.

Disclosures: **L. Galvan:** None. **J. Berg:** None. **J.Y. Chen:** None. **C. Cepeda:** None. **D. Geschwind:** None. **M.S. Levine:** None.

Poster

584. Autism: Synaptic and Cellular Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 584.12/E15

Topic: C.06. Developmental Disorders

Support: Merit Award BX001638

NIH P50 AG033514

NSF Graduate Research Fellowship Program

Title: Neuronal overexpression of AT-1 causes an autistic-like phenotype in the mouse

Authors: *R. HULLINGER[1], L. MI[2], J. WANG[2], E. BOMBA[2], J. DOWELL[2], C. BURGER[2], E. CHAPMAN[2], J. DENU[2], L. LI[2], L. PUGLIELLI[2];
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Abstract: The import of acetyl-coA into the lumen of the ER by AT-1/SLC33A1 is an essential step in the secretory pathway that regulates the N(ε)-lysine acetylation status of ER resident and transiting proteins (J Cell Sci 2010;123:3378; J Biol Chem 2012; 287:22436). Our group has demonstrated that lysine acetylation within the ER is essential for ER mediated quality control. Specifically, properly folded proteins are acetylated and proceed through the secretory pathway, whereas unfolded/misfolded proteins are retained and subjected to ER associated degradation (J Biol Chem 2014;289:46). In addition, our group has shown that decreased activity of AT-1 leads to aberrant autophagy in cell lines (J Cell Sci 2010;123:3378; J Biol Chem 2012; 287:29921), and causes neurodegeneration, inflammation, and propensity to infections and cancer in a mouse model (J Neurosci 2014;20:6772). Heterozygous mutations in AT-1 have been identified in patients affected by autosomal dominant spastic paraplegia-42 (SPG42) while homozygous mutations have been identified in patients affected by severe neurodevelopmental delay and childhood death. Finally, a duplication of AT-1/SCL33A1 has been reported in patients with autism spectrum disorder and intellectual disability. In the present study, we sought to investigate the consequences of increased activity of AT-1. To investigate this, we generated the AT-Tg mouse model that selectively overexpresses AT-1 in neurons. These animals demonstrate cognitive deficits and autistic like social behaviors, aberrations in synaptic plasticity, dramatic enhancements in dendritic spines and branch formation, and widespread proteomic changes. In addition, we found that AT-Tg animals display widespread increases in the expression of mitochondrial enzymes related to acetyl-coA production, suggesting that increased movement of acetyl-coA into the ER causes downstream compensatory mechanisms in mitochondrial activity.

Furthermore, we discovered that AT-Tg animals display epigenetic changes marking global increases in transcription. In conclusion, our results indicate that increased expression of AT-1 can cause an autistic-like phenotype by affecting key neuronal pathways.

Disclosures: **R. Hullinger:** None. **L. Mi:** None. **J. Wang:** None. **E. Bomba:** None. **J. Dowell:** None. **C. Burger:** None. **E. Chapman:** None. **J. Denu:** None. **L. Li:** None. **L. Puglielli:** None.

Poster

584. Autism: Synaptic and Cellular Mechanisms I

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Topic: C.06. Developmental Disorders

Support: Simons Foundation 240069

NINDS HD053862

Title: Excessive Ras-MAPK-dependent synaptic clustering drives enhanced motor learning in the MECP2-duplication mouse model of syndromic autism

Authors: ***R. T. ASH**[1], S. A. BUFFINGTON[2], P. G. FAHEY[2], J. PARK[2], H. LU[2], M. COSTA-MATTIOLI[2], H. Y. ZOGHBI[3], S. M. SMIRNAKIS[1];
[2]Neurosci., [3]Genet., [1]Baylor Col. of Med., Houston, TX

Abstract: We hypothesized that an imbalance between synaptic stability and plasticity could explain the rigid, restricted behaviors and at times savant-like behaviors seen in autism. The goal of our study was to test this hypothesis by linking changes in synaptic plasticity to a robust learning phenotype in an animal model of autism *in vivo*. We found an increase in the stabilization of dendritic spines formed during rotarod motor learning in the mouse model of MECP2 duplication syndrome, a high-penetrance form of syndromic autism. This increased stabilization is mediated entirely by spines that form cooperatively in clusters. The number of clusters formed and stabilized predicts the mutant's enhanced motor learning and memory phenotype. The Ras-MAPK signaling pathway was found to be hyperactive in MECP2-duplication motor cortex specifically after training. Inhibition of Ras-MAPK signaling normalizes clustered spine stabilization and rescues motor learning behavior in mutants. We propose that excessive cooperative stabilization of synaptic clusters driven by hyperactive Ras-MAPK signaling during learning leads to "overfitting" of movement representations that can

improve motor control but poorly generalize -- that is, a rigid and restricted behavioral repertoire -- in this form of syndromic autism.

Disclosures: **R.T. Ash:** None. **S.A. Buffington:** None. **P.G. Fahey:** None. **J. Park:** None. **H. Lu:** None. **M. Costa-Mattioli:** None. **H.Y. Zoghbi:** None. **S.M. Smirnakis:** None.

Poster

584. Autism: Synaptic and Cellular Mechanisms I

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Topic: C.06. Developmental Disorders

Support: NIH Grant R01-MH063232

NIH Grant T32-MH065215

Title: Physiological effects of an ASD-associated mutation in CaMKIIα

Authors: ***J. R. STEPHENSON**, X. WANG, B. C. SHONESY, J. S. SUTCLIFFE, R. J. COLBRAN;
Vanderbilt Univ., Nashville, TN

Abstract: Autism spectrum disorder (ASD) is a common neurodevelopmental disorder that affects 1-2% of the population and involves deficits in social interaction and communication, along with repetitive or stereotyped behaviors and resistance to change in routines. ASD is a predominantly genetic disorder, and roles exist for both common genetic variation and rare, more penetrant risk alleles in contributing to genetic liability. Numerous rare, ASD-associated genetic mutations impact synaptic proteins, indicating that disruptions in the protein networks involved in synaptic development, architecture and plasticity contribute to ASD etiology. Thus, a current major focus is to understand molecular mechanisms that link ASD-associated mutations to disruptions in neuronal signaling pathways that control synaptic transmission. One key regulator of synaptic function is calcium/calmodulin-dependent protein kinase II (CaMKII), which phosphorylates several synaptic substrates and serves a structural role through interaction with diverse CaMKII-associated proteins (CaMKAPs). Our recent proteomic analyses of synaptic CaMKII complexes found that several ASD-linked proteins are associated with CaMKII in the brain (Baucum et al., 2015. ACS Chem Neurosci **6**:615). Here, we confirm that CaMKIIα and Shank3 can be co-immunoprecipitated from co-transfected HEK293 cells. Moreover, a *de novo* mutation in *CAMK2A* –encoding CaMKIIα— was recently identified in an ASD proband in a

whole exome sequencing study (Iossifov et al., 2014. Nature **515**;216) . Our data indicate that this mutation dramatically decreases CaMKIIα substrate phosphorylation, autophosphorylation at key regulatory residues, and interaction with various CaMKAPs. Furthermore, we have found that over-expression of the mutated CaMKIIα in primary hippocampal neurons at different developmental stages causes multiple changes in dendritic morphology. These studies provide novel mechanistic insights into a potential role for CaMKIIα in ASD and will advance our understanding of the impact to synaptic development and function caused by ASD mutations.

Disclosures: J.R. Stephenson: None. **X. Wang:** None. **B.C. Shonesy:** None. **J.S. Sutcliffe:** None. **R.J. Colbran:** None.

Poster

584. Autism: Synaptic and Cellular Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 584.15/E18

Topic: C.06. Developmental Disorders

Title: Neuregulin-1 promotes redox-dependent neuronal cobalamin metabolism by stimulating cysteine-dependent glutathione synthesis

Authors: *R. C. DETH[1], N. HODGSON[2], M. TRIVEDI[1], M. SCHRIER[1], Y. ZHANG[3]; [1]Pharmaceut. Sci., Nova Southeastern Univ., Davie, FL; [2]Neurol., Harvard Med. Sch., Boston, MA; [3]Pharmaceut. Sci., Northeastern Univ., Boston, MA

Abstract: Neuregulin-1 (NRG-1) is a key neurotrophic factor involved in energy homeostasis and CNS development. Impaired NRG-1 signaling is associated with neurological disorders, especially schizophrenia. Cobalamin (Cbl), also known as vitamin B12, is an essential micronutrient which mammals must acquire through diet and neurologic dysfunction is a primary clinical manifestation of Cbl deficiency. Here we show that NRG-1 stimulates neuronal synthesis of bioactive Cbl species adenosylcobalamin (AdoCbl) and methylcobalamin (MeCbl) in SH-SY5Y neuronal cells by both promoting conversion of inactive to active Cbl species and increasing neuronal Cbl uptake. Formation of active Cbls is glutathione (GSH)-dependent and the NRG-1-initiated increase is dependent upon its stimulation of cysteine uptake by excitatory amino acid transporter-3 (EAAT3), leading to increased GSH. The stimulatory effect of NRG-1 on cellular Cbl uptake is associated with increased expression of megalin, which facilitates Cbl transport in ileum and kidney. MeCbl is a required cofactor for methionine synthase (MS) and we demonstrate the ability of NRG-1 to increase MS activity, as well as affecting levels of methionine methylation cycle metabolites. The ability of lithium to promote megalin-related

transport activity has been previously described. Lithium treatment caused a significant increase in cysteine and GSH levels along with an increase in methylation capacity but a decrease in Cbl content. Thus our results identify novel neuroprotective roles for NRG-1 in terms of stimulating antioxidant and Cbl synthesis, as well as novel actions of lithium on redox and methylation status. These findings provide a potential mechanistic link between impaired NRG-1 signaling and neurological disorders such as schizophrenia.

Disclosures: **R.C. Deth:** None. **N. Hodgson:** None. **M. Trivedi:** None. **M. Schrier:** None. **Y. Zhang:** None.

Poster

584. Autism: Synaptic and Cellular Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 584.16/E19

Topic: C.06. Developmental Disorders

Support: NIH Grant B426-5

Title: Neuronal adaptor protein Mint2/APBA2 associated in the pathogenesis of Autism Spectrum Disorders (ASDs)

Authors: ***Y. LIN**[1,2], K. CONNOR[2], A. E. DUPRE[2], G. M. DILLON[2], U. BEFFERT[2], A. HO[2]; [1]Dept. of Pharmacol. and Exptl. Therapeut., Boston Univ. Sch. of Med., Boston, MA; [2]Biol., Boston Univ., Boston, MA

Abstract: Autism Spectrum Disorders (ASDs) comprise a heterogeneous group of neurodevelopmental disorders characterized by a complex genetic etiology. Mutations in the human *MINT2* gene (official gene name, *APBA2*) that encodes for a neuronal adaptor protein have been genetically-linked to ASD patients. In addition, several studies have independently identified copy number variants in the *MINT2* gene associated with ASD. Also, the *MINT2* gene maps to the distal portion of chromosome 15q13.1, a region commonly deleted in Prader-Willi and Angelman syndromes and duplicated in cases of autism, making *MINT2* an attractive candidate gene associated with autism. To date, the functional consequences of these Mint2 variants in neuronal development and physiology have yet to be examined. We hypothesize that Mint2 plays an important role in neuronal development and function. Previous studies have identified seven novel nonsynonymous coding variants in Mint2 in ASD subjects. We found that these Mint2 ASD mutants did not disrupt Mint2 expression; however, three of the Mint2 mutants (R4Q, T660M, and N723S) alter the binding and localization of its interacting partners and affect

Mint2 function. Since ASDs are associated with structural and functional abnormalities in neurons, we examined whether Mint2 ASD mutants altered axon polarization and dendritic branching. We found that the N723S Mint2 ASD mutant decreased axon length and dendritic branching. In addition, we found that the N723S Mint2 ASD mutant decreased the frequency of spontaneous miniature currents of excitatory synapse suggesting that the N723S Mint2 ASD mutant altered neuronal development and synaptic function. In addition to sequence variants, copy number variants of Mint2 may be responsible for severe ASD phenotypes based on the chromosomal location of the *MINT2* gene. Therefore, we examined whether overexpression of Mint2 altered neuronal development. We found that overexpression of Mint2 increased axon length and synaptic density which correlated with the increase in miniature event frequency in excitatory synapses suggesting that Mint2 alters excitatory presynaptic neurotransmitter release machinery. Our results indicate that sequence and copy number variants in Mint2 lead to dysfunction in neuronal development and that altered synaptic function of Mint2 is a potential mechanism that contributes to ASD pathogenesis. A better understanding of the molecular mechanism of how genes affect neuronal physiology will eventually lead to advances in diagnosis and treatment in ASD.

Disclosures: **Y. Lin:** None. **K. Connor:** None. **A.E. Dupre:** None. **G.M. Dillon:** None. **U. Beffert:** None. **A. Ho:** None.

Poster

584. Autism: Synaptic and Cellular Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.06. Developmental Disorders

Support: Malkin Scholars Program from the Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Title: The ependymal protein alpha-T-catenin contributes to autism through its age-dependent effect on ventricle size and neurogenesis

Authors: *S. S. FOLMSBEE, D. R. WILCOX, C. J. GOTTARDI;
Northwestern Univ., Chicago, IL

Abstract: Autism is a complex disease, with a wide variety of clinical presentations and a vast spectrum of neurologic dysfunction. Recently, single nucleotide polymorphisms and copy number variants in the cell-cell adhesion protein alpha-T-catenin has been implicated in the

development of autism, as well as other neurologic disorders with autistic-like behaviors. Even more striking, a recent study found that compound heterozygote mutations in alpha-T-catenin were linked to the development of autism. However, the vast majority of research of alpha-T-catenin is limited to its function in the heart, which is where it is primarily expressed. Although alpha-T-catenin has been found in detectable levels in the brain, the primary cell type expressing it, as well as its potential impact on brain function is unknown. Using an alpha-T-catenin total knockout (KO) mouse, we have found that alpha-T-catenin is indeed present in the brain, localizing to the ependymal cells lining the ventricles, but is absent in the cells of the choroid plexus and neurons. It co-localizes with other cadherin complex members, including N-cadherin and alpha-E-catenin. From immunofluorescence imaging of alpha-T-catenin KO brains, we detect an increase in the expression of alpha-E-catenin in the cell-cell junctions of ependymal cells, as well as a less apical distribution when compared to wild-types (WT). This suggests that the loss of alpha-T-catenin may induce an ependymal cell junction dysfunction, with a compensatory response in other adhesion proteins. Additionally, in the KO mice, there may be changes to the structure and overall presence of motile cilia on ependymal cells, based on a preliminary histologic analysis. There also is increased proliferation in the subventricular zone due to loss of alpha-T-catenin, as well as an increase in ventricle size, both of which are more prominent in aged mice. Most importantly, we have found that alpha-T-catenin KO mice show behaviors consistent with an autism-like phenotype. In mice allowed to age for many months, alpha-T-catenin KO mice show increased self-grooming behaviors when compared to WT, which is an established measure of autism-like behavior in rodent models. Together, our data show that alpha-T-catenin is indeed present in the brain, specifically in the cells lining the ventricles. Furthermore, the loss of alpha-T-catenin in the brain may contribute to autistic phenotypes through dysfunction of ependymal cell-cell adhesion, increase in neurogenesis, and enlargement of the ventricles.

Disclosures: **S.S. Folmsbee:** None. **D.R. Wilcox:** None. **C.J. Gottardi:** None.

Poster

584. Autism: Synaptic and Cellular Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.06. Developmental Disorders

Support: SFARI 306572

Miller Institute for Basic Research in Science

Title: Circuit-level E/I-ratio disruption in ASD mouse models: a common model of sensory hyperexcitability?

Authors: *M. W. ANTOINE[1], P. SCHNEPEL[2], D. E. FELDMAN[2];
[1]Miller Inst. for Basic Res. in Sci., Univ. Of California, Berkeley, Berkeley, CA; [2]Univ. of California Berkeley, Berkeley, CA

Abstract: Given the genetic heterogeneity of autism spectrum disorder (ASD), is there a common pathology at the neural circuit level? A major hypothesis is that ASD involves increased excitation-inhibition (E-I) ratio and hyperexcitability in local neocortical circuits, which may underlie seizure proclivity and hypersensitivity to sensory stimuli. To test this model, we are comparing circuit physiology and sensory processing in primary somatosensory (S1) cortex across multiple ASD mouse strains. S1 is a reasonable site to investigate ASD circuit dysfunction since 80-90% of ASD patients have sensory abnormalities including tactile hypersensitivity. Here, we report initial results from two ASD strains: contactin associated protein-like 2 (Cntnap2) and fragile X mental retardation 1 (Fmr1) mice. Using whole-cell recordings in S1 slices, we measured layer (L) 4-evoked (feedforward) EPSCs and IPSCs converging in single L2/3 pyramidal cells. In Fmr1-/y mice, EPSCs showed a non-significant trend toward reduction by 43% but IPSCs were reduced by 64% relative to controls (n = 17, 17 cells). As a result, E-I ratio in individual neurons was increased by 32%. In CNTNAP2-/- mice, EPSCs were reduced by 62% and IPSCs were reduced by 82% relative to CNTNAP2+/+ littermates (n=12, 12 cells), causing E-I ratio to increase by 40%. Thus, both strains showed a pronounced decrease in inhibition and increased E-I ratio. Reduced inhibition likely reflects reduced function of parvalbumin (PV) interneuron circuits, which mediate L4-L2/3 feedforward inhibition. To test whether these circuit changes affect sensory processing, we recorded in anesthetized Fmr1-/y and FVB mice, but initial data showed no change in L2/3 single unit whisker receptive field width or magnitude of whisker-evoked spiking responses to weak whisker deflections (n = 44, 21 units). Thus, other mechanisms may preserve sensory representations despite altered feedforward excitation, inhibition, and E-I ratio in L2/3 of FmR1-/y mice. Future measurements will assay local circuit excitability, and test additional ASD mouse strains. The long-term goal is to test the E-I ratio hypothesis and reveal what form(s) of circuit dysfunction, if any, are common in sensory cortex across genetically distinct forms of ASD.

Disclosures: **M.W. Antoine:** None. **P. Schnepel:** None. **D.E. Feldman:** None.

Poster

584. Autism: Synaptic and Cellular Mechanisms I

Location: Hall A

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Topic: C.06. Developmental Disorders

Support: SFARI Director's Award

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R25 NS070680-02S1

K12 HD072222-01A1

Title: Convergent excitability defects in the prefrontal corticothalamic circuit unite diverse mouse models of autism

Authors: *A. C. BRUMBACK[1], V. S. SOHAL[2];
[1]Pediatric Neurol., [2]Psychiatry, Univ. of California, San Francisco, San Francisco, CA

Abstract: OBJECTIVE: Autism is one of the most heritable neurodevelopmental disorders, and though many genes have been linked to the condition, how these genetic changes translate into deficits in social interactions is largely unknown. Recent work suggests that defects in diverse genes and signaling pathways associated with autism converge upon the deep layer (L5/6) projection neurons within the prefrontal cortex (PFC). L5/6 of the medial PFC (mPFC) is comprised of at least two distinct classes of pyramidal neurons that project either subcortically (corticothalamic - CT cells) or to the contralateral mPFC (corticocallosal - CC cells). METHODS: We studied the physiology of these two subpopulations of mPFC L5/6 pyramidal neurons in three distinct mouse models of autism: prenatal exposure to valproate (VPA, a commonly used anticonvulsant and histone deacetylase inhibitor), knockout of the Fragile X gene (FMR1, an mRNA binding protein), and knockout of the Contactin Associated Protein-Like 2 gene (CNTNAP2, a cell adhesion molecule). RESULTS: We found that these three diverse autism models exhibit a common circuit-level deficit in prefrontal CT cell excitability. In the autism models, mPFC L5/6 CT cells had depolarized resting membrane potentials, decreased input resistance, and fired fewer action potentials in response to depolarizing current steps. Comparable changes were not seen in CC neurons. Previous work in our laboratory has shown that within the mPFC, D2R expression occurs largely (though not exclusively) within deep layer CT neurons. Therefore, to explore possible behavioral consequences of reduced mPFC CT cell excitability, we optogenetically inhibited D2R-expressing neurons. Surprisingly, acute optogenetic inhibition of D2R-expressing neurons within the mPFC increased social exploration in the VPA-exposure model of autism. CONCLUSIONS: Together, these results demonstrate a specific circuit-level defect in the mPFC associated with multiple etiologically distinct forms of autism. Furthermore, ameliorating abnormal activity in D2R-expressing, thalamically-projecting deep layer prefrontal neurons may represent a novel therapeutic strategy for social defects in

autism spectrum disorders. Supported by NIH and the Simons Foundation Autism Research Initiative.

Disclosures: A.C. Brumback: None. **V.S. Sohal:** None.

Poster

584. Autism: Synaptic and Cellular Mechanisms I

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Topic: C.06. Developmental Disorders

Support: National Medical Research Council Collaborative Basic research grant (NMRC/CBRG/0075/2014)

Khoo Postdoctoral Fellowship Award (Duke-NUS-KPFA/2015/0001)

Title: Identification of rare causal variants in autism spectrum disorder

Authors: *N. HUSAIN[1], I. CUTCUTACHE[2], Q. YUAN[1,3,4], Y. XIAO[1], C. ARCINAS[1], W. YU[5], J. KO[6], A. CHEN[8], C. KIM[7], S. ROZEN[2], H. JE[1];
[1]Program in Neurosci. and Behavioral Disorders, Duke-Nus Grad. Med. Sch., Singapore, Singapore; [2]Ctr. for Computat. Biol., Duke-NUS Grad. Med. Sch., Singapore, Singapore; [3]NUS Grad. Sch. for Integrative Sci. and Engin., [4]Dept. of Physiology,Yong Loo Lin Sch. of Med., Natl. Univ. of Singapore, Singapore, Singapore; [5]Natl. Neurosci. Inst., Res. Dept., Singapore, Singapore; [7]Dept. of Pharmacology, Brain Res. Inst., [6]Yonsei Univ., Seoul, Korea, Republic of; [8]Sch. of Biol. Sci., Nanyang Technological Univ., Singapore, Singapore

Abstract: Autism spectrum disorders (ASDs) are common developmental neurological disorders, characterized by impaired social interaction and communication. Despite significant heritability of ASDs, their extreme genetic heterogeneity has proven challenging for gene discovery. Recent studies have shown that massively parallel sequencing using a targeted gene panel is particularly suited for diagnostic testing for genetically heterogeneous conditions. Therefore, we re-sequenced all the exons of the 700 ASD candidate genes in 500 patients with ASD and 500 control subjects and identified 800 novel missense rare variants in 200 genes. Furthermore, we identified that CDH13 gene, which encodes T-cadherin, showed the highest number of missense/nonsense mutations out of the 700 ASD candidate genes. Intriguingly, gene knockdown of CDH13 using RNA interference (RNAi) in excitatory neurons impaired excitatory synaptic transmission. Expression of wild-type CDH13 could rescue this defective excitatory

synaptic transmission, however, some of the ASD variants could not. Mass spectrometry analyses revealed a novel neuronal binding partner and the potential mechanism that confers the defective synaptic phenotypes by CDH13 knockdown. Our combined approaches will provide additional support to the growing evidence linking the dysfunction of neural cell-adhesion molecules to ASDs.

Disclosures: **N. Husain:** None. **I. Cutcutache:** None. **Q. Yuan:** None. **Y. Xiao:** None. **C. Arcinas:** None. **W. Yu:** None. **J. Ko:** None. **A. Chen:** None. **C. Kim:** None. **S. Rozen:** None. **H. Je:** None.

Poster

584. Autism: Synaptic and Cellular Mechanisms I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 584.21/E24

Topic: F.02. Animal Cognition and Behavior

Title: Developmental *in vivo* cellular localization of Shank1 and Shank2 scaffold proteins

Authors: *S. M. COLLINS, R. GALVEZ, S. REED;
Psychology, Univ. of Illinois, Urbana, IL

Abstract: It is well known that development is a critical period that is in part characterized by remarkable synaptic changes within the neocortex. Anatomical studies have shown that neocortical synapse density and dendritic spine morphology have very distinct developmental patterns. However, the mechanisms underlying these synaptic changes remain elusive. One family of proteins that have been shown to mediate synaptic changes and thus may contribute to these developmental neocortical changes are the Shank family of scaffold proteins. In the brain, these proteins have been shown to be exclusively localized to the post synaptic density (PSD) of excitatory neurons. Studies exploring the role of Shank1 and Shank2 in synaptic plasticity have further demonstrated that genetic modulation of either can change synapse size and density. Furthermore, Shank1 and Shank2 genetic knockouts have been shown to be dramatically impaired on several learning paradigms that have been shown to cause neocortical synaptic plasticity. Similarly, preliminary data from our laboratory has shown an increase in Shank expression in primary somatosensory cortex during acquisition for the associative learning paradigm, whisker trace eyeblink conditioning (WTEB). Our laboratory has previously demonstrated that WTEB transiently increases dendritic spine density in layer IV of primary somatosensory cortex during task acquisition. Collectively, these data suggest that Shank1 and Shank2 play a critical role in both learning-induced and developmental neocortical synaptic

plasticity. However, the developmental expression profile of these proteins are unknown. The present study used immunofluorescence to determine the cell type and localization of Shank1 and Shank2 expression during four developmental time points that cover synaptic development in primary somatosensory cortex. These analyses will provide a better understanding of the role of Shank1 and Shank2 during development of neocortical neuronal properties.

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Poster

585. Autism: Environment and Pathology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 585.01/E25

Topic: C.06. Developmental Disorders

Support: SafeMinds

Title: Involvement of p53 in neurodevelopmental toxicity of mercury and ethanol

Authors: *E. M. SAJDEL-SULKOWSKA;
Psychiatry, Harvard Med. Sch/BWH, Boston, MA

Abstract: Background: Regulation of neuronal stem cells (NSC) proliferation and differentiation is critical for normal neurodevelopment and especially sensitive to the environmental perturbation. Perinatal exposure to environmental toxins, mercury and ethanol (ETOH), has been linked to neurodevelopmental pathologies such as autism spectrum disorders (ASD) and fetal alcohol syndrome (FAS), yet the underlying mechanism(s) are not clear. We have shown previously that exposure of NCS *in vitro* to thimerosal (TM; an ethyl mercury preservative in biological materials), resulted in decreased cell proliferation and changes in expression of genes linked to neuronal survival; exposure of NSC to ETOH *in vitro* has been shown to interfere with cell differentiation. Altered expression of p53, a protein involved in regulation of both cell proliferation and differentiation has been implicated in both mercury- and ETOH-associated cell damage. Aims: The aim of the present study was to probe p53 involvement in neurodevelopmental toxicity of TM and ETOH. Methods: Rat embryonic NSC, and mouse wild type and p53 knockout NCS were cultured in proliferation media (StemCell Technologies). On day 6 in culture, TM (17 nM) or ETOH (100μM) were added to the media and cells were harvested 24hrs later. Additionally, the effect of toxins was measured in rat-P1 cerebellar cultures. Cell proliferation was determined by a direct and nonradioactive proliferation assay (MTT); gene expression was determined by qRT-PCR. Results: We report that the addition of

TM resulted in growth inhibition in rat embryonic NCS (72.5%), mouse wild type NCS (57%) and p53 knockout mouse NCS (38%); addition of TM to primary cultures resulted in growth inhibition and altered expression of genes related to cell survival. The addition of ETOH resulted in no significant effect in rat embryonic NCS, growth inhibition in mouse wild type NCS (79.5%), and in rat primary cultures (59%), but growth stimulation in p53 knockout mice NCS (50.5%). Summary: The results of this study support p53 involvement in the neurotoxity of both TM and ETOH. The data further suggest that p53 signaling pathway may contribute to TM-associated increase in NSC apoptosis, but ETOH-associated decrease in cell proliferation. Indeed, it has been shown that exposure of NCS to ETOH results in decreased expression of mitosis-related genes in p53-signaling pathway. Toxin-associated changes in cell apoptosis and/or cell proliferation may in turn alter the developmental stage-specific progenitor cell number critical for normal development thus contributing to neurodevelopmental pathologies.

Disclosures: E.M. Sajdel-Sulkowska: None.

Poster

585. Autism: Environment and Pathology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 585.02/E26

Topic: C.06. Developmental Disorders

Title: Macroautophagy pathway analysis in autism spectrum disorders

Authors: *A. HAM[1], H. LI[1], S. KUO[1], D. SULZER[2], G. TANG[1];
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Abstract: Autism spectrum disorders (ASDs) are genetically heterogeneous, but different ASD genes may cluster into a smaller number of pathways, including the protein kinase mammalian target of rapamycin (mTOR). mTOR is a key molecule that regulates protein homeostasis by promoting protein synthesis and inhibiting macroautophagy (autophagy thereafter), a homeostatic degradation process whereby cellular proteins and organelles are engulfed by autophagosomes, digested in lysosomes, and recycled to sustain cellular metabolism. We recently discovered that mTOR is overactive in excitatory neurons in brains of a subset of ASD patients [Tang et al., 2014]. Excessive mTOR activity in ASD is associated with a increase in the density of dendritic spine synapses as well as a blockade in dendritic spine pruning, a postnatal developmental process during which unnecessary excessive excitatory synapses are eliminated. Autophagy deficiency in response to the faulty mTOR activity contributes largely to the ASD

synapse pathology. This study aims to screen for autophagy activities in peripheral blood cells and to provide a means to identify a subset of autism for treatment targeting autophagy pathway. We found a significant decrease in autophagy marker LC3II and an increase in autophagy substrate p62 in ASD-derived lymphoblasts, both suggest a low level of basal autophagy. Hyperactivation of mTOR is not seen in all lymphoblasts taken from individuals with ASD (<10 yrs), indicating addition regulatory mechanisms in autophagy impairment in ASD. We thus used the human autophagy RT² Profiler™ PCR array to profile the expression of 84 genes involved in autophagy in both control and autism lymphoblasts. The array includes genes that encode components of the molecular machinery and key regulators modulating autophagy in response to both extracellular and intracellular signals. Among these genes, we found that AMBAR1, Atg9A, ULK1, three genes involved in the formation of autophagic vacuoles and the initiation of autophagy, are downregulated. These transcriptional changes were validated at protein levels by western blot analysis in both ASD lymphoblasts and postmortem human brain. Our data provide further evidence that autophagy is downregulated in ASD, and autophagy-based biomarkers in peripheral lymphoblasts may predict a subset of ASD patients for targeted interventions.

Disclosures: **A. Ham:** None. **H. Li:** None. **S. Kuo:** None. **D. Sulzer:** None. **G. Tang:** None.

Poster

585. Autism: Environment and Pathology

Location: Hall A

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Program#/Poster#: 585.03/E27

Topic: C.06. Developmental Disorders

Support: Autism Speaks and U.S. Army Medical Research and Material Command grant PR100040 (DSB)

Title: Prenatal environmental factors alone can induce autism and epilepsy in a rat model

Authors: *F. M. BERCUM[1], K. M. RODGERS[2], A. M. BENISON[3], Z. Z. SMITH[4], J. TAYLOR[4], E. KORNREICH[4], D. BARTH[4];
[1]UNIVERSITY OF COLORADO, Boulder, CO; [2]Univ. of Colorado at Denver, Denver, CO; [3]St. Jude Med., Denver, CO; [4]Univ. of Colorado at Boulder, Boulder, CO

Abstract: It has long been known that autism spectrum disorder (ASD) is strikingly comorbid with epilepsy, with over 30% of ASD patients also experiencing chronic recurrent seizures and a similar fraction of epilepsy patients with behavioral symptoms of ASD. These numbers rise as high as 60% when sub-convulsive epileptiform spikes are included in assessment of epilepsy.

While the comorbidity of ASD and epilepsy could hold clues to possible common mechanisms for both of these disorders and point the way to intervention strategies, there is a need for animal models to facilitate this work. Here we examined the effects of combining maternal stress with a perinatal teratogen terbutaline (currently used to arrest pre-term labor), both recognized risk factors in humans for ASD in offspring, on both ASD-like behavior (deficits in social exploration and vocalization and enhanced repetitive behavior) and spontaneous recurrent seizures in rats. We found that either treatment alone resulted in a subset of ASD-like behavior (vocalization deficits) and no signs of epilepsy. The combination of maternal stress and terbutaline produced the full triad of ASD-like behaviors and 50% of the rats also developed recurrent convulsive temporal lobe seizures. Furthermore, the remaining half of these animals displayed sub-convulsive spikes in the absence of seizures. We conclude that: 1) Combinations of teratogens are far more powerful than single treatments, a conclusion that should be extended to human studies of risk factors, 2) Both convulsive seizures and non-convulsive epileptiform spikes are closely associated with severe behavioral disturbances associated with ASD, and finally, 3) The present results represent not only a new and highly realistic animal model of epilepsy and ASD, but provide a platform for exploring mechanisms and developing anti-epileptiform/anti-ASD compounds.

Disclosures: F.M. Bercum: None. **K.M. Rodgers:** None. **A.M. Benison:** None. **Z.Z. Smith:** None. **J. Taylor:** None. **E. Kornreich:** None. **D. Barth:** None.

Poster

585. Autism: Environment and Pathology

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Program#/Poster#: 585.04/E28

Topic: C.06. Developmental Disorders

Support: Korea Healthcare Technology R&D Project A111230

National Research Foundation of Korea NRF-2011-0021866

Title: Early behavioral abnormalities and perinatal alterations of Pten/Akt pathway in valproic acid autism model mice

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[1]Seoul Nat'L Univ. Coll. of Med., Seoul, Korea, Republic of; [2]Seoul Nat'L Univ. Coll. of Natural Sci., Seoul, Korea, Republic of; [3]Seoul Nat'L Univ. Bundang Hosp., Seoul, Korea, Republic of

Abstract: Valproic acid (VPA) exposure during pregnancy has been linked with increased incidence of autism, and has been demonstrated as a useful model of autism in mice. We examined the early behavioral and anatomical changes as well as molecular changes in mice prenatally exposed to VPA (VPA mice). In this study, we first showed that VPA mice showed impaired social recognition, developmental delays as assessed with self righting, eye opening and social recognition tests. In addition, we provide the first evidence that primary cultured neurons from VPA-treated embryos present an increase in dendritic spines, compared with those from control mice. Mutations in phosphatase and tensin homolog (PTEN) gene is also known to be associated with autism, and mice with Pten knockout show characteristics of autism. The protein levels of Pten and p-Akt was found to be reduced in the cerebral cortex and the hippocampus, and a distinctive anatomical change in the CA1 region of the hippocampus which is a similar to the Pten knockout model was observed. Taken together, our study suggests that prenatal exposure to VPA induces autistic behavioral and neuroanatomical changes via the reduction of Pten level and these changes were detectable in the early days of life.

Disclosures: **S. Ahn:** None. **U. Mahmood:** None. **J. Ryu:** None. **K. Lee:** None. **H. Kim:** None.

Poster

585. Autism: Environment and Pathology

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Program#/Poster#: 585.05/E29

Topic: C.06. Developmental Disorders

Support: Johnson Center for Child Health and Development

Simons Foundation Autism Research Initiative

DOD grant W81XWH

Title: Blood biomarkers for autism: Peptoids

Authors: *U. YAZDANI[1], S. ZAMAN[1], B. GADAD[1], W. LI[1], N. ROATCH[2], C. SCHUTTE[2], L. HEWITSON[2], D. GERMAN[1];
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Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and social interaction, and restricted, repetitive patterns of behavior, interests or activities that manifest in early childhood. Research findings have

identified widespread changes in the immune system of children with autism, at both systemic and cellular levels. In order to identify individuals with ASD and initiate interventions at the earliest possible age, biomarkers for the disorder are desirable. To identify blood biomarkers of ASD we have used an unbiased screening approach for IgG biomarkers. We have used on-bead displays of thousands of different peptoids (N-substituted oligoglycines) to screen for candidate IgG antibody biomarkers for ASD. We have identified several peptoids (ASD1, ASD19-22) that unexpectedly bind higher levels of IgG in serum from typically developing (TD) boys compared to boys with ASD (n=50/group). The ASD1 peptoid binds >2-fold higher levels of IgG1 in TD serum than in ASD serum. Also, the peptoid-binding levels of IgG1 in the ASD boys is similar to that in older normal men (mean age = 66 years; n=53). In this Training Set of samples, the ASD1 peptoid predicts ASD with an accuracy of 66%. When we combine measurements of thyroid stimulating hormone levels with the ASD1 peptoid values from the same children, the ASD predictive accuracy is increased to 73%. These data suggest that combining peptoid and protein measurements can provide a useful blood biomarker for ASD.

Disclosures: **U. Yazdani:** None. **S. Zaman:** None. **B. Gadad:** None. **W. Li:** None. **N. Roatch:** None. **C. Schutte:** None. **L. Hewitson:** None. **D. German:** None.

Poster

585. Autism: Environment and Pathology

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 585.06/E30

Topic: C.06. Developmental Disorders

Support: Johnson Center for Child Health and Development

Title: Blood biomarkers for autism: Proteins

Authors: ***D. C. GERMAN**[1], S. SINGH[1], U. YAZDANI[1], B. GADAD[1], S. ZAMAN[1], N. ROATCH[2], C. SCHUTTE[2], L. HEWITSON[2];
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Abstract: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and social interaction, and restricted, repetitive patterns of behavior, interests or activities that manifest in early childhood. Research findings have identified widespread changes in the immune system of children with autism, at both systemic and cellular levels. In order to identify individuals with ASD and initiate interventions at the

earliest possible age, biomarkers for the disorder are desirable. To identify blood biomarkers of ASD we have used the Myriad Rules Based Medicine Luminex platform to measure inflammatory proteins in the blood of children with ASD (DiscoveryMAP 175+) (n=30 ASD and n=30 typically develop [TD] boys). We found 11 proteins, 7 of which were significantly different between the two groups (<0.05), that collectively predicted ASD vs. TD. Two of the most important proteins in the panel are interleukin-8 (IL-8) and thyroid stimulating hormone (TSH). These two proteins were cross-validated using the Meso Scale Discovery platform with ASD and TD boys (n=34-51/group; mean age 5 years). TSH levels were 26% lower in the ASD boys, whereas IL-8 levels were significantly higher in the ASD boys. When we used the combined levels of TSH and IL-8 to predict ASD, the predictive accuracy was 82%. These data suggest that a panel of serum proteins can be useful as a biomarker for ASD in boys. Research was supported by the Johnson Center for Child Health and Development.

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Poster

585. Autism: Environment and Pathology

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 585.07/E31

Topic: C.06. Developmental Disorders

Title: Left lateralized sexual dimorphism in cortical thickness in autism

Authors: *A. BEDFORD[1], M. M. PARK[2,3], G. A. DEVENYI[2], R. PATEL[2], M. CHAKRAVARTY[2,4];
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Abstract: Individuals with autism spectrum disorder (ASD) have been shown to have abnormal developmental trajectories of the cerebral cortex. Studies have shown cortical thickness (CT) to be increased in individuals with ASD compared to typical controls, yet results have been inconsistent. These findings have largely been based on male-dominant samples, despite reported differences in behavioural profiles and symptom severity between sexes, and little research has examined sex differences in altered cortical development in ASD. This study aims to identify the differences in cortical thickness between males and females with ASD, relative to healthy controls. MRI scans of 316 subjects (25 females with ASD, 38 female controls, 129 males with

ASD and 124 male controls, ages 6-30) were analysed, using a subset of the Autism Brain Imaging Data Exchange. Due to the disproportionate number of males in the dataset, we included in our analysis only the 3 sites with the largest number of female subjects, and which also used a Siemens Magnetom scanner. CT was estimated using the CIVET pipeline, and multiple linear regression were conducted at 40,962 CT vertices per hemisphere, to model the diagnosis by sex interaction, accounting for the age as a covariate. Correction for multiple comparisons were done using FDR. A diagnosis by sex interaction for CT was observed in the left orbitofrontal cortex, left dorsolateral prefrontal cortex, and left temporal pole, and survived 10% FDR, with the left orbitofrontal cortex also surviving 5% FDR. Males with ASD showed increased CT compared to male controls whereas females with ASD showed a decrease relative to female controls, with the magnitude of the difference in mean CT between the female groups being stronger than in the males. This interaction was significant in the same areas in the right hemisphere only at 15% FDR, indicating a possible left lateralization of the sex differences. Our results suggest that autism manifests differently in males versus females, and indicate the importance of stratifying by sex when studying the neuroanatomy of autism.

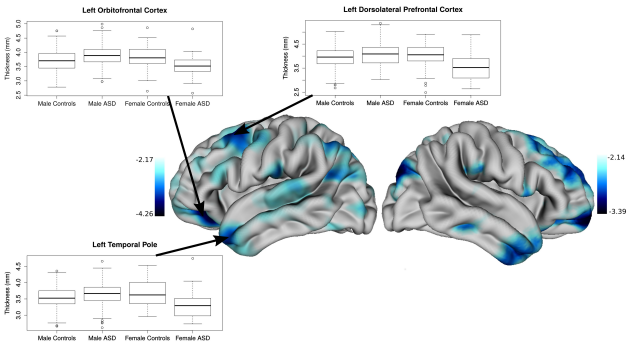

Figure. Diagnosis by sex interaction for cortical thickness in left hemisphere (at 10% FDR) and right hemisphere (at 15%FDR). Colour bars for the left and right hemispheres show the range of t-values displayed, from the FDR threshold to the minimum calculated t-value

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Poster

585. Autism: Environment and Pathology

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 585.08/E32

Topic: C.06. Developmental Disorders

Support: The Deanship of Academic Research at University of Jordan

Title: Dysregulation in metal homeostasis in autistic children compared to controls in jordan

Authors: *L. ALZGHOUL[1], N. ABU TARBOUSH[1], M. ELDAHABI[1], S. ALBDOUR[1], O. ABU HANTASH[2], B. ABU-IRMAILEH[3];
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Abstract: Metals ions play important roles in a variety of essential biological functions, and their homeostasis are generally firmly regulated via a system of metal transporters and binding proteins such as Metallothionein (MT). MT is cysteine rich metal binding protein that plays a role in metals homeostasis by regulating intestinal absorption of essential metals and detoxification of heavy metals. The lack or excess of essential minerals and trace elements are known to cause a variety of health problems, and could contribute to the etiology of Autism spectrum disorder (ASD). In addition, many studies suggest that children with ASD have decreased ability to excrete toxic metals which may play a role in the pathogenesis of ASDs. In human body, zinc (Zn) plays a critical role in cell proliferation, differentiation and signaling especially in the brain. And Zn deficiency has been frequently associated with symptoms that are core ASD. Hence, several studies have suggested the possible involvement of Zn deficiency in the pathophysiology of autism. On the other hand, Copper (Cu) is an essential trace element for living cells, and plays an important role in redox reactions. Although, both Zn and Cu bind to MT and can influences its synthesis by stimulating its gene transcription, nevertheless, Zn and Cu are considered as metabolic antagonists, where their concentrations tend to be inversely related. In the central nervous system, many studies highlighted the role of Zn and Cu in regulating glutamatergic synaptic function, and hence the proper development of the brain. Given the importance of zinc (Zn) and copper (Cu) metabolism for neurological functioning and detoxification of heavy metals, as well as regulating metallothionein levels, the aim of this study was to analyze the Zn, Cu and Cu/Zn ratio as well as MT levels in the blood samples of autistics compared to control kids in Jordan. Serum levels of Zn and Cu were measured using flamed - Atomic absorption and the Cu/Zn ratio was calculated. Furthermore, plasma MT levels were measured using Elisa kit. The Cu/Zn ratio and MT levels of children with ASD were compared with healthy age and sex matched subjects as controls. The preliminary findings of the present study were that: 1) increased Cu/Zn ratio in the serum of autistics compared to controls, and 2) a reduced metallothionein levels was also noted in autistics compared to control. Our present finding implicated the potential link between dysregulation in metal homeostasis as a possible environmental factor for the etiology of ASD. In addition, Cu/Zn ratio may be used as a dependent measure for the functional state of metal homeostasis, and serve as quick and early screening for ASD.

Disclosures: **L. Alzghoul:** None. **N. Abu Tarboush:** None. **M. Eldahabi:** None. **S. Albdour:** None. **O. Abu Hantash:** None. **B. Abu-Irmaileh:** None.

Poster

585. Autism: Environment and Pathology

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Program#/Poster#: 585.09/E33

Topic: C.06. Developmental Disorders

Support: MH097236

Title: Optimization of Golgi impregnation methods for analyses of dendritic complexity in human brain disorders

Authors: *R. K. WEIR[1], M. D. BAUMAN[2], C. M. SCHUMANN[2];
[1]Univ. of California, Davis, Sacramento, CA; [2]UC Davis MIND Inst., Sacramento, CA

Abstract: The amygdala, perhaps more than any other brain region, has been implicated in multiple neurodevelopmental and psychiatric disorders (Schumann et al., 2011). A widely held view is that the amygdala is essential for learning the emotional significance of a stimulus in the environment and coordinating an appropriate response. Aberrant structure and/or function of this system could have profound effects on human social and emotional behavior, which are common components of disorders such as autism and schizophrenia. Studies of amygdala size and volume highlight a difference in the growth trajectories of the amygdala through development from childhood to adulthood in these disorders (Schumann et al., 2004; Levitt et al., 2001). Although the underlying neurobiological mechanisms remain unknown, one hypothesis is that aberrant development of dendrites and synapses leads to improper neuronal connectivity of brain regions responsible for the emotional and social impairments at the core of these disorders. Therefore, our laboratory has focused on investigating neuronal morphology in the human brain of these disorders as well as in animal models. For example, we recently found aberrant dendritic morphology in a nonhuman primate model of brain development in offspring exposed to maternal immune activation (Weir et al., 2015). We have demonstrated successful staining specifically with the Golgi-cox method in our nonhuman primate studies of brains with short-term fixation. However, this method is less effective for staining human tissue that is typically in a fixative for months to several years (Rosoklija et al., 2003). In order to address this issue for our studies of neuron morphology in the human amygdala, we have developed an optimized protocol for staining human brain tissue using a modified version of the Golgi-kopsch technique. In brief, tissue blocks (1.5x1.5x0.8cm) are taken from the amygdala, immersed in solutions of 5% potassium dichromate with 30% formaldehyde (ratio 4:1 parts, 5 days), followed by 0.75% silver nitrate solution (3 days), this is then repeated (5% potassium dichromate (4 days) and 0.75% silver nitrate (2 days). Amygdala tissue blocks are then dehydrated, embedded in parlodion, and cut into 150μm sections. This protocol yields neurons that are well impregnated,

with clearly visible spines, and staining of glial cells is minimal, allowing for data collection on dendritic complexity and spine density. This method allows for the study of neuronal morphology in many neurodevelopmental and psychiatric disorders, including our study of amygdala dendritic arborization and spine density in autism brains compared to typically developing brains.

Disclosures: R.K. Weir: None. **M.D. Bauman:** None. **C.M. Schumann:** None.

Poster

585. Autism: Environment and Pathology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 585.10/E34

Topic: C.06. Developmental Disorders

Support: 5R01NS081208-03

Title: Meta-analysis of region-specific transcriptome changes in the brain of autism patients

Authors: *D. VELMESHEV[1], M. MAGISTRI[2], N. KHOURY[1], M. FAGHIHI[2];
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Abstract: Autism is a neurodevelopmental disorder that affects 1 in every 68 children in the US. Symptomatically, autism is characterized by impaired social interactions, language deficits and repetitive behavior. Autism is a highly hereditary disease, and monozygotic twin studies revealed 90% concordance of autism in twin pairs. More than a hundred genetic loci have been associated with autism, most of them are rare de novo variants. These mutations have been shown to affect several core molecular pathways and cell types, including synaptogenesis and neural development pathways. However, in order to gain a better understand of autism pathogenesis and to develop treatment and prevention strategies, one needs to elucidate how multiple genetic variants converge of common molecular pathways and cause specific behavioral deficits. In order to approach this problem, we investigated whole-transcriptome gene expression changes in autism patients specifically in brain regions relevant to the disease pathology. In particular, we looked at changes that take place in the prefrontal cortex by performing RNA sequencing and bioinformatics analyses, and in the frontopolar prefrontal cortex, Broca's area, frontoinsular cortex, Brodmann area 19 and primary visual cortex using RNA-seq data deposited to National Database for Autism Research (NDAR). Meta-analysis of RNA-seq data revealed multiple genes and pathways dysregulated in the autism brain in a region-specific fashion, as well as common between regions that are involved in performing the same neural and behavioral tasks.

Interestingly, expression of these genes remained unchanged in the primary visual cortex, a region that has not been associated with the disorder. Thus, the candidate genes and pathways may represent true drivers of autism pathogenesis that by altering development, patterning and function of specific brain regions lead to characteristic behavioral abnormalities.

Disclosures: D. Velmeshev: None. **M. Magistri:** None. **N. Khoury:** None. **M. Faghihi:** None.

Poster

585. Autism: Environment and Pathology

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Topic: C.06. Developmental Disorders

Support: NIMHRO1MH094681

Title: Role of prefrontal cortical interneurons in the pathogenesis of autism

Authors: *E. HASHEMI[1,2], J. ARIZA[1,2], V. MARTINEZ-CERDENO[1,2,3];
[1]Inst. For Pediatric Regenerative Med., Sacramento, CA; [2]Pathology and Lab. Med., Univ. of California Davis, Sacramento, CA; [3]MIND Inst., Sacramento, CA

Abstract: The etiology of autism has yet to be determined. One of the important parts of the brain known to be involved in neuropathology of autism is prefrontal cortex (PFC). This region is critical for complex behaviors such as language, social behavior, memory, cognition and decision-making. People with autism display deficits in communication and social interactions that may be due to disruptions in neuronal communication and connectivity in PFC. Electroencephalography (EEG) recordings from the cerebral cortex of autistic patients exhibit an alteration of induced gamma activity patterns. The altered gamma activity pattern in autistic subjects indicates an imbalance in the ratio of excitation/inhibition in cerebral cortex. The cause of this imbalance is poorly understood. Many variants and mutations of different genes cause a disturbance of excitatory/inhibitory balance. Several studies point to alterations in molecular components of inhibitory synapse leading to autism. Postmortem brain tissue showed a reduction of GAD65 and GAD67 enzymes and a lower level of inhibitory GABA receptors in autistic individuals. Therefore, an alteration in the number of each subpopulation of interneurons might be a possible reason for imbalance of excitation/inhibition ratio. The majority of interneurons in the cerebral cortex can be classified in three major subtypes: parvalbumin+ (PV), calbindin+ (CB), or calretinin+ (CR) interneurons. These interneuronal subtypes have distinct morphologies, physiological properties, and connectivity patterns. We hypothesized that an alteration in number

of prefrontal cortical interneurons could explain, at least in part, the altered cognition phenotype present in autism. We quantified the number of interneurons in (Broadmann Area) BA9, A46 and BA47 of prefrontal cortex of autism and age-matched control subjects. Formalin-fixed human brain tissue from 10 individuals with autism and 10 age and sex-matched control subjects were obtained thought the Autism Tissue Program. We quantified the number of interneurons that express CB, CR, or PV, and calculated ratios for the number of interneurons expressing each marker. We found a decrease in PV+ interneurons in BA9, BA46 and BA47. Decreased PV+ interneurons can have an impact on the local and widespread circuit activity and neural communication in the cortex. Determining an alteration of specific subtype of interneurons in autism will address one of the mechanisms that could alter the excitation/inhibition balance in the cerebral cortex.

Disclosures: E. Hashemi: None. **J. Ariza:** None. **V. Martinez-Cerdeno:** None.

Poster

585. Autism: Environment and Pathology

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Program#/Poster#: 585.12/E36

Topic: C.06. Developmental Disorders

Support: NIMH Grant 5R01MH097236-04

Title: Electron microscopic examination of axon density and myelin thickness in temporal lobe white matter in autism

Authors: *T. A. AVINO[1], X.-B. LIU[2], C. M. SCHUMANN[1];
[1]Psychiatry & Behavioral Sci., Univ. of California, Davis MIND Inst., Sacramento, CA; [2]Univ. of California, Davis, Davis, CA

Abstract: Background: Autism is often characterized as a disorder of aberrant cortical connectivity, which has been demonstrated through a number of functional and structural imaging methods. Functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) studies demonstrate desynchronized and disrupted cortical communication in autism. Additionally, diffusion tensor imaging (DTI) and structural MRI scans show abnormal growth trajectory and loss of white matter fiber integrity in autism particularly within the temporal lobes. However, the microanatomical mechanisms that underlie this large-scale deficit are relatively unknown and limited. **Objectives:** The goal of the present study was to assess the ultrastructural characteristics of axons within the temporal lobe white matter in individuals with autism relative

to their age-matched neurotypical counterparts. **Methods:** White matter from the superior temporal gyrus and fusiform gyrus was dissected from autistic and age-matched neurotypical subjects from 50µm frozen sections. The samples were prepared for ultrathin sectioning and electron microscopic analysis according to Schumann & Liu (2014). Myelinated axons were randomly selected for g-ratio analysis and imaged at high magnification (8,400x) whereby the myelin sheath thickness is calculated relative to the axon diameter. Data regarding the overall density and size distribution was acquired at medium magnification (4,800x) across 20 images (10µm x10µm each) per subject per region. **Results:** Consistent with previous reports, results from the g-ratio analysis indicate decreasing proportional myelin thickness with increasing axon diameter in both autistic and neurotypical subjects. However, these data show thinner myelination patterns across all axon sizes in the adult autistic subjects relative to their neurotypical counterparts. In addition, the individuals with autism show a lower density of axons across all axon sizes. These effects are present in both cortical regions but are more pronounced in the fusiform gyrus. **Conclusion:** The data are consistent with similar reports of alterations to reduced myelin thickness in areas of the frontal lobe in autism (Zikopolous & Barbas, 2010) and may contribute to increased diffusivity of the white matter. When taken together with the decrease in axon density across all axon sizes in the temporal lobe in autism, the results provide a basis for the observed neuronal communication deficit in the disorder at the ultrastructural level.

Disclosures: **T.A. Avino:** None. **X. Liu:** None. **C.M. Schumann:** None.

Poster

585. Autism: Environment and Pathology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 585.13/E37

Topic: C.06. Developmental Disorders

Support: NIH grant 5R01MH093348

NIH grant P50HD055751

Title: Increased binding of MeCP2 and DNMT1 to RELN and GAD1 regulatory regions is associated with down-regulation of RELN and GAD1 mRNAs in postmortem prefrontal cortex of autism spectrum disorder (ASD) brain

Authors: ***A. ZHUBI**[1,2], Y. CHEN[3], E. DONG[3], E. H. COOK[3], A. GUIDOTTI[3], D. GRAYSON[3];

[1]Psychiatry, Univ. Ill at Chicago, Chicago, IL; [2]CHOICES Behavioral Hlth., OSF St. Elizabeth Med. Ctr., Ottawa, IL; [3]Psychiatry, Univ. of Illinois at Chicago, Chicago, IL

Abstract: Autism Spectrum Disorder (ASD) is neurodevelopmental condition characterized by symptoms related to social interactions/communication and restricted and repetitive behaviors. The ethiopathogenesis of ASD involves a dynamic interplay between environmentally-induced epigenetic mechanisms acting on numerous genes, including those identified in genome-wide association studies. We have focused our work on DNA writers (DNA methyltransferases and TET-cytosine dioxygenases) and readers (Methyl Binding Domain proteins) of these DNA marks. We are interested in the down-regulation of GAD1 and RELN and epigenetic modifications of the corresponding promoters of these genes. We used a small cohort of post-mortem human prefrontal cortex obtained from the Harvard Brain Tissue Resource with permission of the Autism Tissue Program. These include 11 control (CON) and 10 ASD subjects. We performed chromatin immunoprecipitation (ChIP) to measure the levels of binding of MeCP2 and DNMT1 to the GAD1, GAD2, and RELN promoters and gene bodies. We also performed methyl DNA- and hydroxymethyl-DNA immunoprecipitation to measure total 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC) in the promoters of these genes. Real time qPCR was used for quantification and values were expressed as a percent of input DNA. We observed a significant (1.5-2 fold) decrease in the mRNAs corresponding to GAD 1 ($p=0.02$,t-test) and RELN ($p=0.03$,t-test) in ASD vs CON. In addition, MECP2 binds significantly more (>2 fold) to the promoters of GAD1 ($p=0.002$), GAD 2 ($p=0.006$) and RELN ($p=0.001$) in PFC of ASD. Similarly, DNMT1 binds significantly more (>2 fold) to the promoters of GAD1 ($p=0.006$), GAD 2 ($p=0.015$) and RELN ($p=0.028$) in FC of ASD. Interestingly, we observed a significant decrease in the GAD1 and RELN 5mC promoter levels and little change in the amounts of 5hmC in these genes in ASD. The increased binding of DNMT1 is likely the result of increased unmodified cytosines, which are recognized by the -CXXC- domain of DNMT1. The increased binding of MECP2 is not consistent with the altered levels of 5mC (or 5mC/5hmC ratio) at GAD1 and RELN and may be the consequence of either alternatively spliced variants or post-translational modifications of MECP2 that occur in ASD subjects.

Disclosures: A. Zhubi: None. **Y. Chen:** None. **E. Dong:** None. **E.H. Cook:** None. **A. Guidotti:** None. **D. Grayson:** None.

Poster

585. Autism: Environment and Pathology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 585.14/E38

Topic: C.06. Developmental Disorders

Title: Examination of cell count and size within the superficial layers in autism

Authors: *A. T. KARST[1], J. J. HUTSLER[2];
[1]Univ. of Wisconsin, Oshkosh, Oshkosh, WI; [2]Psychology, Univ. of Nevada, Reno, Reno, NV

Abstract: Neurons in the superficial layers of the human cerebral cortex are involved in long-range cortico-cortical connections. These layers are of interest in studying the neuropathology of autism, as they could potentially play a role in altered connectivity between distal regions of cortex. Evidence for altered connectivity has been demonstrated with both functional as well as anatomical data (Just et al 2007, Hutsler & Zhang, 2010). Of particular interest to this study was whether differences in cell number and/or size were present in superficial layers II and III in individuals with autism in regions of cortex known to be implicated in terms of connectivity. Differences in cell size, specifically smaller cell size in individuals with autism, have been previously observed in particular layers of BA24b (Simms et al, 2009), BA44, and BA45 (Jacot-Descombes, 2012). Using an objective method to classify lamina transitions in Nissl stained tissue, regions of layers II and III for BA7, BA9, & BA21 were isolated and analyzed using a semi automated two-dimensional analysis for cell number and cell size. Analysis of cell number revealed differences for cortical layer and area, but no difference between individuals with autism as compared to control subjects was found. The analysis of cell size again revealed an effect of cortical layer and area, but this analysis additionally revealed a difference of diagnosis as well. The difference in diagnosis indicated that the cell size in individuals with autism were smaller than those of the controls.

Disclosures: A.T. Karst: None. **J.J. Hutsler:** None.

Poster

585. Autism: Environment and Pathology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 585.15/E39

Topic: C.06. Developmental Disorders

Support: NYU Challenge Grant 2014-15

Title: Neuronal streaming in the temporal cortex of control and autism children and adults

Authors: *E. C. AZMITIA[1], Z. T. SACCOMANO[2];
[1]Biol. 1009 Silver Bldg, NYU/ NYUMS, New York, NY; [2]Psychology, NYU, NY, NY

Abstract: Autism is a pervasive development disorder that is characterized by a wide spectrum of disorders and abnormalities in many brain structures. Evidence of disruption in neurogenesis, dysgenesis and migration are found in young autism brains (Courchesne, 1997; Wegiel et al, 2010). It is generally assumed that new neurons migrate from the ventricular zone into the cortical plate during early fetal development and then differentiate into the six layers of cortex before birth. However, up to the age of 18 months, corridors of migrating neurons extend from the ventricular zone through the white matter into the prefrontal cortex (Sanai et al, 2011). In our studies, cortical migratory streams were seen in adults as old 20 years of age. The postmortem brains were obtained from the Brain Bank for Disabilities and Aging in Staten Island, Harvard Brain Tissue Rep and the NICHD Brain and Tissue Bank for Developmental Disorders at University of Maryland, Baltimore. All autism patients were diagnosed using the Autism Diagnostic Interview-revised (ADIr) before death. The average age for the autism group (n =10; 14.5 yrs., range 2.8-28 yrs.) is similar to the control group (n = 10; 15.1 yrs., range 1.8-32 yrs.). Brain sections (50um) of the temporal lobe including the superior temporal gyrus were immunocytochemically stained with antibodies against vimentin, actin, GFAP and MAP-2 with DAB as substrate. GFAP-positive varicose fibers, a uniquely human trait, are seen extending down from the pia layer and up from the white matters at all ages. Vimentin-positive neurons are seen in layers II-VI at all ages in STG with more neurons in the deeper layers of autism brains. Actin positive neurons extend long dendrites from deep cortical layers towards layer I with more neurons in the upper layers in controls. Finally, MAP-2 positive neurons having a fusiform shape are seen streaming in the white matter and extending into the cortical layers at all ages. There are more MAP-2 positive neurons in the STG white matter at 20.8 yr in autism compared to 20.5 yr control. Quantitative comparisons between control and autism suggest an extended period of development in the autism brain. These results are consistent with the greater number of serotonin axons and angiogenic blood vessels previously seen in autism compared to control.

Disclosures: E.C. Azmitia: None. **Z.T. Saccomano:** None.

Poster

585. Autism: Environment and Pathology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 585.16/E40

Topic: C.06. Developmental Disorders

Support: INMED funds and INSERM

Neurochlore

Fondation Bettencourt Schueller

France's Agence Nationale de la Recherche ANR-12-RPIB-0001-01

France's Agence Nationale de la Recherche ANR-14-CE13-0021-01

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Fellowship CIFRE-ANRT (2014/1056)

Title: The effect of bumetanide treatment in rodent models of autism

Authors: *D. C. FERRARI[1], R. NARDOU[1], M. CHIESA[1,2], N. LOZOVAYA[1], S. EFTEKHARI[2], R. TYZIO[2], M. BILLON-GRAND[1], N. BURNASHEV[2], Y. BEN-ARI[1,2]; [1]Neurochlore, Marseille, France; [2]INMED, INSERM U901, Aix-Marseille Univ., Marseille, France

Abstract: GABAergic signals are altered in autism and GABA-acting benzodiazepines exert paradoxical effects in patients with autism suggesting that, as in epilepsies, GABA excites neurons because of elevated intracellular concentrations of chloride. Indeed, we have recently shown that the oxytocin-mediated neuroprotective GABA excitatory-inhibitory shift during delivery is abolished in the valproate and fragile X rodent models of autism (Tyzio et al, 2014). During delivery and subsequently, hippocampal neurons in these models have elevated intracellular chloride levels, increased excitatory GABA, enhanced glutamatergic activity and elevated gamma oscillations. Maternal pretreatment with bumetanide restored in offspring control electrophysiological and behavioral phenotypes (Tyzio et al, 2014; Eftekhari et al, 2014). Our results suggest a chronic deficient chloride regulation in these rodent models of autism. We aim to elucidate if this deficient chloride regulation is a general feature of autism independently of the mutation, and if it can be restored by bumetanide treatment. Therefore we tested these alterations in the Shank3 KO mouse model of autism and the results will be presented.
References: Tyzio et al, Science (2014) 343, 675; Eftekhari et al, Science (2014) 346, 176.

Disclosures: D.C. Ferrari: A. Employment/Salary (full or part-time):; Neurochlore. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurochlore. **R. Nardou:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurochlore. **M. Chiesa:** A. Employment/Salary (full or part-time):; Neurochlore. **N. Lozovaya:** A. Employment/Salary (full or part-time):; Neurochlore. **S.**

Eftekhari: None. **R. Tyzio:** None. **M. Billon-Grand:** A. Employment/Salary (full or part-time):; Neurochlore. **N. Burnashev:** None. **Y. Ben-Ari:** A. Employment/Salary (full or part-time):; Neurochlore. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurochlore.

Poster

586. Rett Syndrome

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 586.01/E41

Topic: C.06. Developmental Disorders

Support: NIH grant MH085802

the Simons Foundation

the Human Frontier Science Program (HFSP) Fellowship

Title: Human and Mouse Models of Rett Syndrome exhibit altered prenatal cortical development due to alterations in neurogenesis

Authors: *P. IP[1], N. MELLIOS[1], D. FELDMAN[1], S. D. SHERIDAN[2], S. KWOK[1], B. ROSEN[1], B. CRAWFORD[1], Y. LI[3], R. JAENISCH[3], S. J. HAGGARTY[2], M. SUR[1]; [1]Picower Inst. for Learning and Memory, MIT, Cambridge, MA; [2]Ctr. for Human Genet. Res., Cambridge, MA; [3]Whitehead Inst. for Biomed. Res., Cambridge, MA

Abstract: Rett Syndrome (RTT) is a neurodevelopmental disorder that, in the vast majority of cases, arises from mutations in the X-linked gene MECP2. MeCP2 is an epigenetic modulator of gene expression that has recently been shown to interact with miRNA machinery. In addition, MeCP2 itself has been implicated in several neurodevelopmental disorders. Multiple lines of evidence point to the importance of miRNA-mediated pathways downstream of MeCP2 in different stages of brain development and plasticity. We hypothesized that the pleiotropic effects of MeCP2 in prenatal development are mediated via a set of early regulated miRNAs. Towards that end, we used induced pluripotent stem cell (iPSC) RTT lines generated from patients, virally-mediated knockdown of MeCP2 in human embryonic stem cells (ESCs), TALEN-derived isogenic ESC RTT lines, and an Mecp2 mutant mouse model as complementary approaches to identify novel MeCP2-regulated miRNAs and examine their respective influence on neurogenesis and neuronal differentiation.. Via BrdU pulse labelling, we found that the proliferation rate of patient-derived and MeCP2-deficient neuronal progenitor cells was

significantly altered relative to control cells; this was accompanied by reductions in the expression of early neuronal markers and immature dendritic morphology. Our findings to date implicate aberrant regulation of prenatal neurogenesis as a result of MeCP2 deficiency. Taken together, our data support a novel miRNA-mediated pathway downstream of MeCP2 capable of influencing neurogenesis via interactions with central molecular hubs linked to autism spectrum disorders. Ongoing experiments are focused on elucidating the mechanisms of disease-related impairments in neurogenesis in both mouse and human organoid models of RTT, and translating these findings to scalable assays for novel therapeutic discovery

Disclosures: **P. Ip:** None. **N. Mellios:** None. **D. Feldman:** None. **S.D. Sheridan:** None. **S. Kwok:** None. **B. Rosen:** None. **B. Crawford:** None. **Y. Li:** None. **R. Jaenisch:** None. **S.J. Haggarty:** None. **M. Sur:** None.

Poster

586. Rett Syndrome

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 586.02/E42

Topic: C.06. Developmental Disorders

Support: SFB665

Title: Role of BDNF signaling in synapse formation and maintenance in MeCP2Null/y excitatory neurons

Authors: ***C. SAMPATHKUMAR**, Y.-J. WU, T. TRIMBUCH, C. ROSENMUND; Charité - Universitätsmedizin Berlin, Berlin, Germany

Abstract: Methyl CpG-binding protein 2 (MeCP2) is a transcriptional regulator whose loss-of-function mutations result in neurodevelopmental disorders such as Rett syndrome. Prior studies reported that either loss or doubling of MeCP2 results in reduced or increased synaptic output and glutamatergic synapse number, respectively. This study aims to understand the role of MeCP2 in regulating synapse formation in excitatory neurons and the significance of optimal brain-derived neurotrophic factor (BDNF) signaling in maintaining neuronal function in MeCP2 mutant neurons. We investigated morphology of hippocampal glutamatergic autapses derived from *Mecp2*$^{Null/y}$ and *Mecp2*^{Tg1} *mice and observed abnormal axonal and dendritic outgrowth, and reduced somata in Mecp2*$^{Null/y}$ *neurons. However, doubling of MeCP2 did not influence neurite outgrowth as evident from normal axon and dendrite development in Mecp2*^{Tg1} *neurons. To understand the role of BDNF signaling in this context, we overexpressed BDNF in Mecp2*$^{Null/y}$

autaptic neurons and found a significant rescue of synapse number and dendrite outgrowth as well as evoked excitatory postsynaptic currents (EPSCs) and readily releasable vesicle pool (RRP) without affecting release efficiency. This dramatic rescue was reverted back to Null/y levels upon either neutralizing BDNF function or application of Tropomyosin receptor kinase B (TrkB) antagonist, confirming that BDNF induced TrkB signaling is essential for normal neuronal function in Mecp2$^{Null/y}$ neurons. Taken all together, this study demonstrates the importance of BDNF signaling in maintenance of excitatory synapses in MeCP2 mutant neurons at single-cell level. Furthermore, this shows that regulation of BDNF could contribute in part to the pathophysiology of Rett syndrome.

Disclosures: C. Sampathkumar: None. **Y. Wu:** None. **T. Trimbuch:** None. **C. Rosenmund:** None.

Poster

586. Rett Syndrome

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 586.03/E43

Topic: C.06. Developmental Disorders

Support: IRSF-2824

R01-NS065027

R21-HD074418

Title: The TrkB ligand LM22A-4 rescues hippocampal LTP and Rett-like behavioral phenotypes in Mecp2 knockout mice

Authors: *W. LI[1], T. YANG[2], F. LONGO[2], L. POZZO-MILLER[1];
[1]Neurobio., The Univ. of Alabama At Birmingham, Birmingham, AL; [2]Neurol. and Neurolog. Sci., Stanford Univ., Stanford, CA

Abstract: Rett syndrome (RTT) is an autism-linked disorder caused by loss-of-function mutations in the gene encoding methyl-CpG-binding protein 2 (MeCP2), a transcriptional regulator that modulates expression of many genes, including the neurotrophin Bdnf. BDNF deregulation accounts for many sensory, motor, and cognitive deficits in RTT individuals, as well as in mouse models that recapitulate RTT phenotypic traits. We previously demonstrated that naïve hippocampal CA3->CA1 synapses are potentiated in slices from male Mecp2 KO mice, thus saturating long-term potentiation (LTP) (WL & LP-M, SfN 2014). Restoration of

BDNF function has a great potential to rescue these features, but BDNF's inability to across the blood-brain barrier has limited its pharmacotherapeutic use for systemic/peripheral treatment. Here, we used the small molecule LM22A-4, which has sufficient brain penetration and pharmacokinetics, and mimics BDNF signaling by occupying the binding pocket of the BDNF receptor TrkB (Massa et al. 2010). We treated female Mecp2 heterozygous (Het) mice at 4 months of age with LM22A-4 for 2 months (twice daily i.p. injections). Western immunoblots of hippocampal homogenates confirmed the activation of TrkB receptors and downstream signaling pathways in LM22A-4-treated Mecp2 Het mice. The general behavioral phenotype score, open field test, and dowel crossing test all showed significant improvements in locomotor activity and motor coordination in LM22A-4-treated Mecp2 Het mice. At the end of the 2-month treatment, acute slices were used for simultaneous electrophysiology and voltage-sensitive dye (VSD) imaging. Basal transmission at CA3->CA1 synapses and evoked spatio-temporal spread of VSD signals in area CA1 were enhanced in Mecp2 Het mice compared to age-matched female wildtype (WT) controls. In addition, LTP of fEPSPs and VSD signals were smaller in female Mecp2 slices than in WT slices. The 2-month LM22A-4 treatment reduced basal synaptic transmission and the spatio-temporal spread of VSD signals to WT levels, and restored LTP of fEPSPs and VSD signals to levels comparable to those observed in WT slices. Our findings provide preclinical evidence that the BDNF loop-domain mimetic LM22A-4 improves hippocampal function and RTT-related behavioral deficits, thus establishing the rationale for the treatment of RTT and other neurodevelopmental disorders with autistic features associated with MeCP2 dysfunction.

Disclosures: **W. Li:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Frank Longo, PharmatrophiX. **T. Yang:** None. **F. Longo:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); PharmatrophiX. **L. Pozzo-Miller:** None.

Poster

586. Rett Syndrome

Location: Hall A

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Program#/Poster#: 586.04/E44

Topic: C.06. Developmental Disorders

Support: RSRT

NS41590

NS45523

NS49553

NS075672

Jane and Lee Seidman Fund for CNS Research

Title: Partial rescue of Rett syndrome phenotypes via modulation of NF-κB signaling and vitamin D supplementation in Mecp2-null mice

Authors: *J. L. MACDONALD[1,2], N. KISHI[1,3], J. D. MACKLIS[1];
[1]Stem Cell and Regenerative Biol., Harvard Univ., Cambridge, MA; [2]Dept. of Biol., Syracuse Univ., Syracuse, NY; [3]Lab. for Marmoset Neural Architecture, RIKEN Brain Sci. Inst., Saitama, Japan

Abstract: Mutations of the transcriptional regulator MeCP2 cause the X-linked autism spectrum disorder Rett syndrome (RTT), and MeCP2 has been implicated in several other neurodevelopmental disorders. Our previous results identified that cortical callosal projection neurons (CPN) increasingly express MeCP2 as they mature, and that loss of *Mecp2* function reduces their dendritic complexity in a largely cell autonomous manner. Focusing on CPN, we investigated genes and signaling pathways that function downstream of MeCP2 in cerebral cortex circuitry, and identified *Irak1*, a signaling kinase and scaffold protein within the NF-κB pathway. We confirmed that *Irak1* is up-regulated following *Mecp2* loss-of-function, and that over-expression of *Irak1* recapitulates the reduced dendritic complexity phenotype of *Mecp2*-null CPN, both *in vitro* and *in vivo*. We established that NF-κB pathway signaling is up-regulated with loss of *Mecp2* function or *Irak1* over-expression in cortical neurons. Importantly, we found that genetic attenuation of the aberrant NF-κB signaling in *Mecp2*-null mice not only ameliorates the CPN dendritic complexity phenotype, it significantly extends (~50%) the usually shortened lifespan of *Mecp2*-null mice. These results indicate that abnormal activation of NF-κB signaling is critically involved in RTT-like cortical dysgenesis, dendritic complexity, and reduced lifespan of *Mecp2*-null mice, and that NF-κB pathway modulation might offer a therapeutic target in RTT. There are many known inhibitors of NF-κB, including the hormone vitamin D. Interestingly, we identified that *Mecp2*-null mice, like many RTT patients, are vitamin D deficient. We investigated potential therapeutic treatment of *Mecp2*-null mice by dietary supplementation of vitamin D, and identified dose-dependent amelioration of CPN dendritic complexity and reduced soma size phenotypes, as well as a modest increase in lifespan. These results provide new insight into both the fundamental neurobiology of RTT, and potential therapeutic strategies via NF-κB pathway modulation.

Disclosures: J.L. MacDonald: None. **N. Kishi:** None. **J.D. Macklis:** None.

Poster

586. Rett Syndrome

Location: Hall A

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Topic: C.06. Developmental Disorders

Support: Supported by the Cluster of Excellence and DFG Research Center Nanomicroscopy and Molecular Physiology of the Brain (CNMPB), and the International Rett Syndrome foundation (IRSF).

Title: Chronic *in vivo* treatment of Rett mice with the free radical scavenger Trolox

Authors: O. A. JANC, M. A. HUESER, K. CAN, B. KEMPKES, *M. MUELLER;
Univ. Goettingen, Goettingen, Germany, Germany

Abstract: Rett syndrome (RTT) is a severe neurodevelopmental disorder affecting almost exclusively girls. After a normal development for the first year of life, complex and severe disease symptoms start to manifest. They include pronounced cognitive impairment, epilepsy, motor dysfunction, and potentially life-threatening breathing disturbances with intermittent systemic hypoxia. Mitochondria seem to be affected as well. Mouse models of Rett syndrome (MeCP2-deficient mice) replicate several of these symptoms. Rating mitochondrial function in male Rett mice (Mecp2-/y) revealed an intensified mitochondrial respiration, a less efficient cellular redox homeostasis, and an oxidative burden. Interestingly, these alterations become evident already at neonatal and presymptomatic stages. Therefore, they may critically contribute to the manifestation of typical RTT symptoms and/or facilitate disease progression. *In vitro*, we confirmed that the free radical scavenger Trolox, a vitamin E derivative, dampens neuronal hyperexcitability, reinstates synaptic plasticity, ameliorates cellular redox balance, and improves hypoxia tolerance in the isolated hippocampus of adult, symptomatic Mecp2- /y mice. Therefore, we now performed a placebo-controlled blinded systemic treatment of Mecp2- /y mice with Trolox, starting at very young, presymptomatic stages. To ensure most reliable compound dosing and administration, we performed intraperitoneal injections of either saline, 10 or 40 mg Trolox/kg body weight. Trolox-treated Mecp2- /y mice showed a normalization of blood glucose levels. Furthermore, low doses of Trolox improved the hypoxia-tolerance and synaptic short-term plasticity of Mecp2- /y hippocampus. Lipid peroxidation in cortical tissue samples was also less pronounced in Trolox treated mice. Systemic Trolox treatment did, however, not improve body weight or size, the regularity of breathing, motor function and learning, or exploratory behavior of Mecp2-/y mice. Rather, the frequent animal handling and intraperitoneal injections dampened some of the phenotypic differences among WT and Mecp2-/y mice, which may have masked potential merits of Trolox. In conclusion, our findings show that radical scavengers may be promising for the treatment of various aspects in RTT. However,

the very route of compound administration and the frequency of animal handling are critical parameters to be optimized in further trials.

Disclosures: **O.A. Janc:** None. **M.A. Hueser:** None. **K. Can:** None. **B. Kempkes:** None. **M. Mueller:** None.

Poster

586. Rett Syndrome

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Topic: C.06. Developmental Disorders

Support: Rettsyndrome.org

SFARI Simons Foundation

Research Grant for RIKEN OSC from MEXT to YH

Research Grant from MEXT to RIKEN CLST

Title: CAGE analysis of genes involved in the onset of Rett Syndrome

Authors: *A. PATRIZI[1], C. LI[1], A. FORREST[2], E. ARNER[2], P. CARNINCI[2,3], A. SAXENA[2,4], M. FAGIOLINI[1];
[1]Neurol., Boston Children's Hosp. Harvard Med. Sch., Boston, MA; [2]Omics Sci. Ctr. (OSC), 1-7-22 Suehiro cho, Tsurumi ku, Omics Sci. Center, RIKEN Yokohama Inst., Yokohama, Japan; [3]Div. of Genomic Technologies (DGT), RIKEN Ctr. for Life Sci. Technologies, Yokohama, Japan; [4]Biomed. Res. Ctr. at Guy's and St Thomas' Trust, Genomics Core Facility, Guy's Hosp., London, United Kingdom

Abstract: Mutations of the MECP2 gene cause Rett syndrome (RTT) and related autism spectrum disorders (Amir et al., 1999). MECP2 encodes a methyl-CpG-binding protein that has been proposed to function as a transcriptional repressor and activator. Despite numerous studies examining gene expression in murine models of RTT, it is still unknown which genes are first misregulated in the absence of Mecp2, leading to the onset of RTT phenotype. We recently discovered that Mecp2-null mice exhibit loss of visual function that correlates with onset of RTT phenotype (Durand et al., 2012). Here, we used Cap Analysis of Gene Expression (CAGE; Vitezic et al., 2014) to identify the changes in gene expression that underlie such regression. We analyzed the transcriptome of the visual cortex of Mecp2-null mice in comparison with wild-type

(WT) littermate controls at three developmental ages: eye opening (postnatal day 15; P15), peak of critical period plasticity (P30) and adulthood P60. Our data reveal no differentially expressed transcripts at the beginning of visual cortical development, P15, well before the onset of RTT phenotype. On the contrary, at the beginning of visual regression, P30, we identified 54 differentially regulated transcripts in the Mecp2-null mice. By P60, when Mecp2-null animals are severely visually impaired, we found 844 differentially regulated transcripts. Most of these genes were involved in neuronal connectivity and communication, metabolism and intracellular signaling. Our data identify the biological pathways perturbed in the visual cortex of Mecp2-null mice, before and after the onset of symptoms. Our study demonstrates the utility of CAGE in the investigation of genetic disorders. RIKEN Omics Science Center ceased to exist as of April 1st, 2013, due to RIKEN reorganization.

Disclosures: **A. Patrizi:** None. **C. Li:** None. **A. Forrest:** None. **E. Arner:** None. **P. Carninci:** None. **A. Saxena:** None. **M. Fagiolini:** None.

Poster

586. Rett Syndrome

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Program#/Poster#: 586.07/E47

Topic: C.06. Developmental Disorders

Support: Translational Research Project, Boston Children's Hospital

NIH U54 HD061222

Title: Visual evoked potentials detect cortical processing deficits in Rett syndrome patients

Authors: J. J. LEBLANC[1,2], G. DEGREGORIO[1], V. K. VOGEL-FARLEY[1], K. BARNES[1], W. E. KAUFMANN[1,2], *M. FAGIOLINI[3,2], C. A. NELSON[1,2,4];
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Abstract: Rett syndrome (RTT) is a neurodevelopmental disorder caused by mutation of the X-linked MECP2 gene and characterized by developmental regression during the first few years of life. Studies in the visual system of mouse models of RTT revealed impaired cortical processing with progression of the disorder using visual evoked potentials (VEP). The objective of this study was to investigate if the VEP can be used as an unbiased, quantitative biomarker to

monitor brain function in RTT patients. We recorded pattern-reversal VEPs in 34 girls with RTT and 20 typically developing controls (2-9 years old) using a low spatial frequency phase-reversing checkerboard stimulus. Girls with RTT exhibited a significant decrease in VEP amplitude that was most striking in the later stages of the disorder. RTT patients also displayed a slower recovery from the principal peak of the VEP response that was impacted by MECP2 mutation type. Visual acuity was also assessed in patients by modulating the spatial frequency of the stimulus. We found that patients displayed a deficit in discriminating smaller patterns, indicating lower visual spatial acuity in RTT, consistent with findings in Mecp2 knock-out mice. VEP is a method that can be used to assess brain function across species and in children with severe disabilities like RTT. Our findings support the introduction of standardized VEP analysis in clinical and research settings to probe the neurobiological mechanism underlying functional impairment and to longitudinally monitor progression of the disorder and response to treatment.

Disclosures: **J.J. LeBlanc:** None. **G. DeGregorio:** None. **V.K. Vogel-Farley:** None. **K. Barnes:** None. **W.E. Kaufmann:** None. **M. Fagiolini:** None. **C.A. Nelson:** None.

Poster

586. Rett Syndrome

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 586.08/E48

Topic: C.06. Developmental Disorders

Support: Rettsyndrome.org

TRP BCH

Title: Ketamine ameliorates visual evoked potential impairments in Mecp2 Heterozygous female mice

Authors: *E. CENTOFANTE, A. PATRIZI, N. PICARD, M. FAGIOLINI;
Neurol., Boston Children's Hosp., Boston, MA

Abstract: Rett Syndrome (RTT), a neurodevelopmental disorder, is caused by de novo mutation of MECP2 gene on X- chromosome and it is characterized by regression during the first few years of life. Recently, we have demonstrated that Mecp2-null mice exhibit impaired visual cortical processing that can be rescued by targeting NMDA receptor (NMDAR) expression and function. These results raise the questions whether 1) a similar defect is present in Mecp2 heterozygous (Het) female mice which are considered a closer model of the human condition;

and 2) administration of NMDAR antagonist ketamine can ameliorate cortical function in RTT. Here, we performed visual evoked potential (VEP) in adult Mecp2 Het that exhibited either mild or severe RTT-like symptoms, according to the 12-point RTT phenotypic score (Guy et al., 2001). Mecp2 Het mice displayed a significant decrease in the amplitude of VEP response in comparison with their wild-type (WT) littermates. Interestingly, such defect was already present in Mecp2 Het mice with mild symptomatology and worsened with the disorder progression. Moreover, VEP response to high spatial frequencies was lost, resulting in a shift down in the spatial frequency (SF) tuning curve and significantly lower spatial resolution. We then tested whether administration of low dosage of NMDAR antagonist, ketamine (8mg/kg, ip) for six weeks (two weeks on/two weeks off) was sufficient to ameliorate the visual function in Mecp2 Het mice. Interestingly, we found an increase in the VEP amplitude in comparison with the Het treated with vehicle. In addition, we observed this increase in the response to all stimuli resulting in an amelioration of the visual acuity. Together our results indicate that visual processing is impaired across Mecp2 mouse models and provide further evidence that targeting NMDAR function is a feasible and an effective therapeutic treatment for Rett Syndrome.

Disclosures: **E. Centofante:** None. **A. Patrizi:** None. **N. Picard:** None. **M. Fagiolini:** None.

Poster

586. Rett Syndrome

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 586.09/F1

Topic: C.06. Developmental Disorders

Support: The Simons Foundation

International Rett Syndrome Foundation

NIH

Title: Post-critical period Mecp2 de-silencing rescues aberrant visual circuits in a Rett syndrome mouse model

Authors: *A. J. SIMON[1,2], N. PICARD[2], M. TAYLOR[2], M. STANLEY[2], C. CHEN[2], M. FAGIOLINI[2];
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Abstract: Rett syndrome (RTT), a neurodevelopmental disorder that results from *de novo* mutations in the MECP2 gene, is characterized by an initial apparently normal period of development followed by regression of motor, respiratory, and sensory functions. Growing evidence points to improper wiring of both excitatory and inhibitory synaptic circuits as the underlying cause. Remarkably, murine studies have demonstrated that motor and respiratory phenotypes can be reversed by late re-expression of *Mecp2*. However, it remains unclear whether sensory impairments can also be rescued. Uniquely, sensory circuits are only amenable to modification in response to external sensory experience during restricted critical periods in early postnatal life. Once windows of plasticity close, proper re-wiring is limited, if not impossible. Here we test 1) whether sensory system abnormalities in Mecp2 mouse models are reversible and 2) if the lateral geniculate nucleus (LGN) and the visual cortex (V1) are similarly sensitive to the loss and re-expression of *Mecp2* in $Mecp2^{loxstop/y}$ x Cre-ESR mice after tamoxifen administration. As in $Mecp2^{-/y}$ mice, we found that visual cortical circuits are indeed significantly impaired before the onset of the general RTT phenotype. Thalamic deficits such as eye specific segregation, conversely, appeared at a much later time point and well after those in primary visual cortex. Strikingly, de-silencing of *Mecp2* after the critical period for visual system plasticity was sufficient to allow recovery of key features of single-unit activity including spontaneous activity and maximal evoked activity at preferred orientations in visual cortical neurons. Furthermore, decreased response reliability of neurons in V1 can similarly be recovered by re-expressing *Mecp2* after this critical period. Our results indicate that cortical circuits are more sensitive to the absence of *Mecp2* than those in the LGN and that they can also be rescued in adulthood.

Disclosures: **A.J. Simon:** None. **N. Picard:** None. **M. Taylor:** None. **M. Stanley:** None. **C. Chen:** None. **M. Fagiolini:** None.

Poster

586. Rett Syndrome

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Topic: C.06. Developmental Disorders

Support: HD062553

NS066601

NS043124

Title: Loss of MeCP2 causes urological dysfunction and contributes to death by kidney failure in mouse models of Rett Syndrome

Authors: *C. S. WARD[1], T.-W. HUANG[2], J. HERRERA[3], R. C. SAMACO[4], M. PITCHER[3], J. L. NEUL[1];
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Abstract: Rett Syndrome (RTT) is a neurodevelopment disorder characterized by loss of acquired skills during development, autonomic dysfunction, and an increased risk for premature lethality. Clinical experience identified a subset of individuals with RTT that present with urological dysfunction including individuals with frequent urinary tract infections, kidney stones, and urine retention requiring frequent catheterization for bladder voiding. To determine if urological dysfunction is a feature of RTT, we queried the Rett Syndrome Natural History Study, a repository of clinical data from over 1000 individuals with RTT and found multiple instances of urological dysfunction. We then evaluated urological function in a mouse model of RTT and found an abnormal pattern of micturition. Both male and female mice possessing Mecp2 mutations show a decrease in urine output per micturition event. Furthermore, we identified signs of kidney failure secondary to urethral obstruction. Although genetic strain background significantly affects both survival and penetrance of the urethral obstruction phenotype, survival and penetrance of urethral obstruction do not directly correlate. We have identified an additional phenotype caused by loss of MeCP2, urological dysfunction. Furthermore, we urge caution in the interpretation of survival data as an endpoint in preclinical studies, especially where causes of mortality are poorly characterized.

Disclosures: C.S. Ward: None. **T. Huang:** None. **J. Herrera:** None. **R.C. Samaco:** None. **M. Pitcher:** None. **J.L. Neul:** None.

Poster

586. Rett Syndrome

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Topic: C.06. Developmental Disorders

Support: R01-NS-073875

Title: Neuronal hyperexcitability versus breathing abnormality in Mecp2-null mice

Authors: W. ZHONG, N. CUI, C. JOHNSON, M. F. OGINSKY, S. ZHANG, Y. WU, *C. JIANG;
Georgia State Univ., Atlanta, GA

Abstract: Neuronal hyperexcitability versus breathing abnormality in *Mecp2*-null mice Zhong W, Cui NR, Johnson MC, Oginsky FM, Zhang S, Wu Y, Jiang C. Department of Biology, Georgia State University, 100 Piedmont Avenue, Atlanta, GA 30303 Rett Syndrome (RTT) is a neurodevelopmental disorder caused mostly by disruptions in the *Mecp2* gene. Breathing abnormality is a characteristic of the disease, which contributes to the high rate of sudden death and brain development. The breathing abnormality is found in *Mecp2*-null mice, involving neurons in the locus coeruleus (LC). LC neurons in *Mecp2*-null mice show inadequate release of norepinephrine (NE), defects in CO2 chemosensitivity and hyperexcitability. The latter has been found in several other types of neurons in *Mecp2*-null mice as well. To understand the relationship of LC neuronal excitability with breathing, we perform studies in which LC neuronal excitability was quantitatively analyzed with breathing frequency (f) variation and apnea in wild-type and *Mecp2*-null mice at various ages. Our results showed that LC neuronal excitability increased with ages in *Mecp2*-null mice. So did the severity of breathing abnormality. Pearson analysis showed a strong correlation of LC excitability with age ($r = 0.70$, $P < 0.001$), apnea rate ($r = 0.84$, $P < 0.001$), and breathing frequency variation ($r = 0.58$, $P < 0.05$). Consistently, *Mecp2*-null LC neurons showed an age-dependent reduction in GABAergic synaptic inhibition as indicated by IPSC frequency and amplitude. The extrasynaptic $GABA_AR$ agonist THIP at a non-sedative dosage reduced LC neuronal hyperexcitability, alleviated breathing abnormalities, and expanded the lifespan of *Mecp2*-null mice. Therefore, these results strongly suggest that the Mecp2 disruption causes age-dependent deterioration in neuronal hyperexcitability together with breathing abnormalities, and stabilization of neuronal excitability benefits breathing and the lifespan of *Mecp2*-null mice.

Disclosures: W. Zhong: None. **N. Cui:** None. **C. Johnson:** None. **M.F. Oginsky:** None. **S. Zhang:** None. **Y. Wu:** None. **C. Jiang:** None.

Poster

586. Rett Syndrome

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NIH Grant P30HD024064 (BCM IDDRC)

Title: Alterations in MeCP2 dosage within dopaminergic neurons regulate startle and prepulse inhibition in mice

Authors: *S. SORIANO[1], D. R. CONNOLLY[2], C. S. WARD[3], C. M. MCGRAW[4], N. M. TRUONG[2], A. CHAHROUR[2], A. J. LIANG[2], H. Y. ZOGHBI[2], J. L. NEUL[3], R. C. SAMACO[2]; [1]Jan and Dan Duncan Neurolog. Res. Inst., Baylor Col. of Med., Houston, TX; [2]Mol. and Genet., Baylor Col. of Medicine/Jan and Dan Duncan Neurolog. Res. Inst., Houston, TX; [3]Neurosciences, Div. of Child Neurol., UCSD, San Diego, CA; [4]Neurol., Univ. of California, San Francisco, San Francisco, CA

Abstract: Abnormalities in sensorimotor gating are prominent in neuropsychiatric disorders. For example, enhanced PPI has been reported in autism spectrum disorders (ASD) cases; in contrast, reduced PPI is a hallmark feature of schizophrenia (SCZ). Interestingly, basal acoustic startle response and prepulse inhibition (PPI) are oppositely affected in mouse models lacking or overexpressing the transcriptional modulator MeCP2, demonstrating a similar contrast to findings in ASD and SCZ. Given the role of the dopaminergic system in regulating aspects of motor function in *Mecp2* mouse models and its link to the modulation of sensorimotor gating, we set out to test the consequences of genetically manipulating MeCP2 expression within tyrosine hydroxylase (TH)-positive cells on acoustic startle and PPI. Using an allelic series of TH-positive conditional knock-out, conditional restoration, and conditional over-expression mice, we demonstrate that basal startle response is directly correlated with the level of MeCP2 dosage within this specific cellular population, and is dependent on the ongoing function of MeCP2 in adulthood. However, changes in PPI do not appear to directly correlate with MeCP2 dosage and is not affected by deleting MeCP2 in adult animals, suggesting that the neural circuits regulating startle and sensorimotor gating in MeCP2 mouse models may operate under separate cellular and developmental mechanisms. Ongoing studies aim to determine whether the expression of genes known to be implicated in startle and PPI are altered within TH-positive according to MeCP2 dosage. Taken together, these findings demonstrate the importance of cell specific MeCP2 dosage in sensorimotor gating and underscore the critical role of MeCP2 in modulating a specific phenotype commonly impaired in many neurological and neurodevelopmental disorders.

Disclosures: S. Soriano: None. **D.R. Connolly:** None. **C.S. Ward:** None. **C.M. McGraw:** None. **N.M. Truong:** None. **A. Chahrour:** None. **A.J. Liang:** None. **H.Y. Zoghbi:** None. **J.L. Neul:** None. **R.C. Samaco:** None.

Poster

586. Rett Syndrome

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Topic: C.04. Neurodegenerative Disorders and Movement Disorders

Support: NIH Grant NS078771

NIH Grant NS040408

Title: Increased GFAP levels accompany neuronal loss in a mouse model of MeCP2 duplication syndrome

Authors: *J. M. FRANKLIN, L. WANG, S. R. D'MELLO;
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Abstract: Methyl-CpG-binding protein 2 (MeCP2), is a protein expressed from the X-chromosome that binds to methylated DNA, modifying chromatin structure to a transcriptional repressed state through the recruitment of co-repressors and histone deacetylases. More recently, it has been found to also activate gene expression by binding to promoters. Increased MeCP2 function resulting from gene duplication (or triplication) causes a distinct neurological disorder called MeCP2 duplication syndrome characterized by severe mental retardation, hypotonia, macrocephaly, epilepsy, progressive spasticity, and premature death. Little is known about molecular and cellular mechanisms underlying MeCP2 duplication syndrome. We are studying this disorder using a transgenic mouse model in which the locus containing the human MeCP2 gene is inserted on the X-chromosome. These mice (designated as MeCP2-Tg) recapitulate the neurological phenotype of patients with MeCP2 duplication syndrome and produce MeCP2 at about 3 times the normal amount. We have found that MeCP2-Tg mice display highly elevated GFAP expression within the hippocampus and cortex, but not in other brain parts starting at 12 weeks of age. Intriguingly, increased GFAP expression seems to be unconnected with neuroninflammation as we have found that the morphology of the astrocytes is similar to that of WT astrocytes and typical resting/non-reactive astroglia. Furthermore, we do not detect any changes in the number of microglia or the morphology of resting microglia. Moreover, we have also found that death of MeCP2 mice is preceded by neuronal loss in the hippocampus and cortex. We have found that the number of NeuN-positive neurons in the MeCP2-Tg mice are comparable to WT mice at 6 weeks of age; however, at 15 weeks of age there is a significant reduction in the NeuN-positive neurons in the cortex and hippocampus but not in the cerebellum. To confirm this, we used two other antibodies, CTIP2 and SATB2, which stain deep layer and superficial cortical neurons, respectively. Indeed, we have detected a reduction in SATB2 and CTIP2-positive neurons in the cortex. Based on our current evidence, we propose that MeCP2 duplication disorder is a neurodegenerative disorder.

Disclosures: **J.M. Franklin:** None. **L. Wang:** None. **S.R. D'Mello:** None.

Poster

586. Rett Syndrome

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Topic: C.06. Developmental Disorders

Support: IRG Marie Curie 248284

Title: IGF1 treatment in RTT patients improve social and cognitive abilities in an open label study

Authors: ***D. TROPEA**[1,2], F. SCUSA[2], N. MORTIMER[1], A. BENINCASA[2], G. PINI[2]; [1]Trinity Col. Dublin, Dublin, Ireland; [2]Versilia Hosp., Tuscany Ctr. for Rett Syndrome, Lido di Camaiore (LU), Italy

Abstract: Rett syndrome (RTT) is a devastating neurodevelopmental disorder that has no cure. After 6-18 months patients show regression of acquired skills, motor and speech impairment, cardio-respiratory distress, microcephaly and stereotyped hand movements. The majority of RTT patients display mutations in the gene that codes for the Methyl-CpG binding protein 2 (MeCP2). Clinical observations and neurobiological analysis of mouse models suggest that defects in the expression of MeCP2 protein compromise the development of the central nervous system, especially synaptic and circuit maturation. Thus, agents that promote brain development and synaptic function are good candidates for ameliorating the symptoms of RTT. In particular, Insulin-like growth Factor 1 (IGF1) and its active peptide (1-3)IGF1 cross the Blood Brain Barrier, and therefore are ideal treatments for neurodevelopmental disorders, including RTT (Tropea et al., 2009). Indeed, both (1-3)IGF1 and IGF1 treatment significantly ameliorates RTT symptoms in a mouse model of the disease (Tropea et al., 2009; Castro et al., 2014). In a previous study we established that IGF1 is safe and well tolerated in Rett patients (Pini et al., 2012). In this study we assessed the social and cognitive abilities of 9 RTT patients treated with IGF1 and 10 untreated controls. Two independent observers blind to the identity of treated individuals observed footages of patients recorded in identical conditions at two different time points: T0 and T1-which corresponds to the pre-treatment and post-treatment phases for the treated patients-and comparable time for untreated controls. They evaluated the ability of the patients to interact with people and environment as well as the negative features of RTT and assigned a score from 1 to 5, where 1 represents heavy RTT and 5 absence of RTT. Even considering that this was an open labeled study, we find a significant improvement in the

cognitive and social abilities of the treated patients but not of the untreated controls. We find no differences in the performances of patients treated with antiepileptic medications. These results have applications to other pathologies considering that IGF1 has been shown to be effective in other disorders of the autism spectrum.

Disclosures: **D. Tropea:** None. **F. Scusa:** None. **N. Mortimer:** None. **A. Benincasa:** None. **G. Pini:** None.

Poster

586. Rett Syndrome

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Topic: C.06. Developmental Disorders

Support: NIH Grant HD073631

NIH Grant HD064817

Title: Neuron-microglia interaction contributes to Rett syndrome pathology

Authors: ***M. HORIUCHI**, L. J. SMITH, I. MAEZAWA, L.-W. JIN;
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Abstract: Rett syndrome (RTT) is an autism spectrum disorder primarily affecting girls. The patients develop normally until 6 to 18 months of age, when they start showing loss of neurodevelopmental milestones, motor and cognitive impairments, autistic features, seizures, and respiratory dysfunction. RTT is largely caused by loss-of –function mutations in the X-linked gene encoding methyl-CpG-binding protein 2 (MeCP2), an epigenetic regulator. Mecp2 knockout (Mecp2KO) mice exhibit RTT-like abnormalities and provide a valid animal model of human RTT. Recovering wild-type (WT) MeCP2 in either neurons or microglia in Mecp2KO mice ameliorated RTT-like abnormalities, suggesting a pathological role of neuron-microglia interaction. CX_3CR1, a chemokine receptor expressed by microglia, mediates neuron-microglia interaction by binding its ligand CX_3CL1 expressed by neurons. While CX_3CR1-CX_3CL1 signaling regulates microglia activation in neuroinflammation, it plays an important role in synaptic pruning during development. Given that Mecp2KO microglia constitutively produce high levels of neurotoxic mediators such as glutamate and reactive oxygen species, we hypothesized that neuron-microglia interaction mediated by CX_3CR1-CX_3CL1 signaling may detrimentally affect neuronal and synaptic integrity in RTT. To test this hypothesis, we

determined the phenotype of Mecp2KO mice with CX_3CR1 ablation. We found that CX_3CR1 ablation significantly improved the RTT-like phenotype presented by Mecp2KO mice, including life span, body weight, the incidence of apneas, and motor coordination. These phenotypic improvements were associated with restorations of the number and morphological complexity of microglia, the production ofinsulin-like growth factor 1 by microglia, and the size of hippocampal CA2 neurons. Our results suggest a deleterious contribution of neuron-microglia interaction to RTT pathogenesis. CX_3CL1-CX_3CR1 signaling, therefore, could be a candidate therapeutic target for RTT.

Disclosures: **M. Horiuchi:** None. **L.J. Smith:** None. **I. Maezawa:** None. **L. Jin:** None.

Poster

586. Rett Syndrome

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Topic: C.06. Developmental Disorders

Support: NIH grant HD064743

NIH grant HD00352

Title: Misregulation of alternative splicing in a mouse model of Rett syndrome

Authors: R. LI[1], Q. DONG[2], C. CHIAO[3], H. LI[2], *Q. CHANG[4];
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Abstract: Mutations in human MECP2 gene cause Rett syndrome (RTT), a severe neurodevelopmental disorder that predominantly affects girls. Despite of decades of work, the molecular mechanism underlying how mutations of this methylated DNA binding protein leads to disease is still largely unclear. To systematically understand the molecular function of MeCP2, we performed coimmunoprecipitaton (Co-IP) on the cortex of FLAG-tagged Mecp2 knock-in mice followed by mass spectrometry to identify physiologically relevant MeCP2-interacting proteins. Gene ontology analysis showed that proteins identified were enriched with transcriptional factors and splicing regulators. MeCP2 has been well-characterized as a transcriptional regulator while its role in regulating splicing is less well defined. Therefore we focused our studies on these novel MeCP2-interacting splicing regulators. Further validation demonstrated that MeCP2 physically interacted with more splicing regulators than previously

appreciated. To illustrate the functional consequence of loss of MeCP2 on alternative splicing, we performed deep RNA sequencing and found that hundreds of splicing events were mis-regulated in Mecp2 null cortex. We are currently in the process of validating some of these changes by independent methods. In order to understand how MeCP2 regulates alternative splicing, we will perform chromatin immunoprecipitation (ChIP) to examine whether MeCP2 binds to these exons and recruits some of its interacting splicing regulators to modulate splicing. We will also test the hypothesis that MeCP2 might regulate alternative splicing through slowing down the progression pace of PolII and hence facilitating the inclusion of the alternative exon. Taken together, we are pursuing to understand better the role of MeCP2 in regulating alternative splicing through interacting with multiple splicing factors.

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Poster

586. Rett Syndrome

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Support: Dorrance Center for Rare Childhood Disorders at TGen.

Title: Transcriptional profiling of Mecp2 A140V mouse model for Rett syndrome/X-linked mental retardation reveals subtle changes in long gene expression

Authors: *S. RANGASAMY[1,2], B. GERALD[1], S. SVEJDA[1], A. HILBERT[1], S. OLFERS[3], G. JENTARRA[4], W. LIANG[1], V. NARAYANAN[1,2];
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Abstract: The molecular mechanisms that lead to typical autism spectrum disorder (ASD) are unknown. Study of single gene disorders (Rett syndrome, Fragile X syndrome, tuberous sclerosis complex, PTEN mutation syndromes) characterized by autistic features, may contribute to the understanding of ASD. Rett syndrome (RTT), an X-linked dominant neurological disorder caused by mutation of the Mecp2 gene, is characterized by stereotyped hand movements and autistic features. We have created a mouse model (MeCP2 A140V "knock-in" mutant) expressing a human Mecp2 mutation linked to an X-linked mental retardation phenotype/Rett syndrome. The major neuropathological findings in the A140V mouse are (a) increased cell

packing density and small soma size), and (b) reduced dendrite branching (3). This exactly recapitulates the key pathological findings in Rett syndrome patients. Molecular evidence suggests that MeCP2 acts as a global transcriptional repressor but emerging evidences indicate that they also activate gene expression. In this study, we explored global gene expression in wild-type and Mecp2 A140V mutant mice and identify the signaling pathways that are affected by Mecp2 mutation. mRNA profiling was performed using affymetrix mouse expression array in layer 4/5 cortical pyramidal neurons of 2-week old male mice (MeCp2 A140V & WT). Changes in transcript levels were assessed by microarray analysis on an individual basis and the molecular pathway network analysis was done using GeneGo Pathways Software. The results of the microarray analyses indicated less dramatic changes in the transcription level of many genes in Mecp2 A140V mice compared to wild type. We observed that among the list of altered expression, 56 percent genes were found to be up-regulated compared to 44 percent down regulation. In addition, our preliminary analysis with gene length in 2 week old mutant mice found that increased expression of small group of long genes related to synaptic function. Gene ontology analysis revealed a significant alteration of multiple pathways in Mecp2 A140V mice comparing to control mice. Genes involved in pathways such as neurogenesis, neuronal differentiation and development were significantly altered. Interestingly, of the several hundred genes with altered expression levels in the mutants, we found that IGF-1 pathway genes implicated in the pathogenesis of Rett syndrome are significantly downregulated. This result suggests that MeCP2 A140V mutation leads to moderate gene expression changes affecting neuro developmental pathway and synaptic function, which may be associated with the phenotypic changes observed.

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Poster

586. Rett Syndrome

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Topic: C.06. Developmental Disorders

Support: NIMH Grant F30MH105087

Title: Alterations in the novel object recognition circuit following MeCP2 deletion from cholinergic neurons

Authors: *E. BALLINGER[1], C. SCHAAF[2], D. TALMAGE[1], H. Y. ZOGHBI[2], L. W. ROLE[1]; [1]SUNY At Stony Brook, Port Jefferson Station, NY; [2]Baylor Col. of Med., Houston, TX

Abstract: Rett Syndrome (RTT) is an autism spectrum disorder that affects approximately 1 in 20,000 girls and is caused by mutations in the gene encoding methyl CpG binding protein 2 (*MeCP2*). The cholinergic system appears to be particularly important in RTT, as decreases in cholinergic markers have been correlated with increased clinical severity in patients with RTT. Schaaf and Zoghbi have developed a powerful transgenic mouse model, whereby *MeCP2* is selectively deleted in cholinergic neurons only, to facilitate study of the contribution of this cholinergic lesion to the overall phenotype of RTT. Interestingly, this model exhibits a selective deficit in recognition memory, a form of declarative memory that has been shown by lesion and electrophysiological studies to be dependent upon cholinergic signaling in the perirhinal cortex (PRH). This memory deficit may map onto the intellectual disability seen in patients with RTT, however, its circuit level electrophysiological underpinnings are unknown. We use *in vivo* electrophysiology to compare baseline firing characteristics of PRH neurons in both mice in whom *MeCP2* has been selectively deleted in cholinergic neurons (*MeCP2* sKO) and control. We also use optogenetics to selectively activate cholinergic neurons in the Nucleus Basalis of Meynert, the cholinergic source nucleus that innervates the PRH, while simultaneously recording the effects of this selective activation to evaluate the cholinergic response profile of the PRH in each genetic condition. The network consequences of this altered responsiveness are evaluated using genetic markers of activity to map the recognition memory engram in both controls and *MeCP2* sKO. We have shown that PRH units of control mice exhibit long time course correlations which are absent in PRH units from *MeCP2* sKO mice, in whom PRH unit firing is more stationary. Given the role of ACh as a neuromodulator, this change may represent deficient modulation of firing. Our recognition memory engram mapping shows that 3-6 times as many PRH cells are activated during exposure to a novel object than are activated during recognition of a familiar object, which is consistent with prevailing models suggesting that recognition is dependent upon modulation of PRH unit excitability. The deficient cholinergic modulation of PRH unit firing that we have observed among *MeCP2* sKO mice may thereby impair encoding of the recognition memory engram and lead to the observed behavioral deficits. These results will further understanding of the role of ACh in encoding recognition memory and of the circuit level perturbations that may underlie cognitive phenotypes seen in patients with RTT.

Disclosures: E. Ballinger: None. **C. Schaaf:** None. **D. Talmage:** None. **H.Y. Zoghbi:** None. **L.W. Role:** None.

Poster

586. Rett Syndrome

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Rett Syndrome Research Trust

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R01NS057819

Howard Hughes Medical Institute

Title: Chronic forniceal deep brain stimulation recuses the impairment of contextual fear memory and hippocampal LTP in Rett syndrome mice

Authors: *S. HAO[1,2], Z. WU[1,2], B. TANG[1,2], Y. SUN[2,3], H. ZOGHBI[1,2,3,4,5], J. TANG[1,2]; [1]Dept. of Pediatrics, Baylor Col. of Medici, Houston, TX; [2]Jan and Dan Duncan Neurolog. Res. Inst., Texas Children's Hosp., Houston, TX; [3]Dept. of Mol. and Human Genet., [4]Dept. of Neurosci., Baylor Col. of Med., Houston, TX; [5]Howard Hughes Med. Inst., Houston, TX

Abstract: Rett syndrome (RTT) is a postnatal neurodevelopmental disorder, which is caused by loss-of-function of X-linked gene encoding methyl CpG binding protein 2 (MeCP2). Cognitive deficit is one of the most reproducible and reliable outcome measures among RTT mouse models. Deep brain stimulation (DBS) serves as an established therapy for several neurological disorders, and recently it has shown promise for ameliorating cognitive deficits as well. Studies in AD patients and in amnestic rats have demonstrated that DBS in the fimbria-fornix, the region that appears to regulate hippocampal activity, reduces memory decline and improves cognitive function. Accordingly, we hypothesized that stimulation of the fimbria-fornix will improve cognitive function in RTT mice. We studied the effects of chronic forniceal DBS in both wide type (WT) and female MeCP2+/- mice, a well-characterized RTT model with impairment of hippocampal memory and synaptic long-term potentiation (LTP). We found that two-week chronic DBS enhanced contextual, but not cue, fear memory in both WT and RTT mice compared with sham controls, respectively. In parallel, forniceal DBS enhanced *in vivo* LTP in the perforant path - dentate pathway in RTT mice and WT littermates. Forniceal DBS boosted contextual memory and LTP in RTT mice to the levels of WT sham controls. As a result, DBS rescues the impairment of contextual memory and hippocampal LTP. These results suggest that chronic forniceal DBS may improve hippocampus-dependent cognitive dysfunction in MeCP2+/- mice via modulation of the hippocampal synaptic plasticity. Stimulating the neural circuits that underlie learning and memory may serve as a therapeutic intervention to enhance cognitive function of developmental neurological diseases.

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Poster

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Topic: C.06. Developmental Disorders

Support: NIH Grant R01-NS065027

IRSF Grant 3117

Title: Bidirectional homeostatic synaptic plasticity is impaired in cultured hippocampal neurons from Mecp2 knockout mice

Authors: ***X. XU**, L. POZZO-MILLER;
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Abstract: Rett syndrome (RTT) is a progressive autism spectrum disorder caused by loss-of-function mutations in the gene encoding methyl-CpG-binding protein 2 (MeCP2). Numerous studies in animal models of RTT have revealed dysfunctions of neuronal and network excitability in Mecp2 deficient mice. Negative-feedback homeostatic synaptic plasticity (HSP), also known as synaptic scaling, maintains the global synaptic strength of individual neurons in response to sustained alterations in neuronal activity. Since the excitation/inhibition balance is impaired in the hippocampus of Mecp2 knockout (KO) mice (Calfa et al. 2015), and thought to be maintained by homeostatic mechanisms, we examined the role of MeCP2 in HSP. HSP was induced by either silencing with tetrodotoxin (TTX) or over-excitation with bicuculline (Bic) for 48hs in hippocampal cultures from male Mecp2 KO and WT littermate pups. Numbers of excitatory synapses and the surface levels of postsynaptic GluA1 were determined by triple color immunocytochemistry of VGLUT1-expressing presynaptic terminals on dendritic spines of GFP-expressing neurons. Here we show that Mecp2 KO neurons have fewer excitatory synapses, higher surface GluA1 and presynaptic VGLUT1 levels than WT neurons. TTX induced an increase whereas Bic induced a decrease of GluA1 and VGLUT1 levels in WT neurons, without changes in the numerical density of GluA1/VGLUT1 puncta. Chronic silencing of Mecp2 KO neurons didn't show scaling-up of GluA1 and VGLUT1 levels; and their over-excitation failed to scale-down GluA1 levels. Intriguingly, Bic scaled-down VGLUT1 levels in Mecp2 KO neurons, as observed in WT neurons. To directly measure synaptic scaling, we recorded miniature

excitatory postsynaptic currents (mEPSC) in pyramidal WT and Mecp2 KO neurons. We found mEPSC are larger, more frequent, and with higher channel conductance in Mecp2 KO neurons than in WT neurons. Chronic silencing of WT neurons increased the amplitude, frequency, and channel conductance of mEPSCs, whereas their over-excitation decreased mEPSC amplitude and the number of channels. On the other hand, TTX failed to scale-up mEPSC amplitude and channel conductance, whereas Bic failed to scale-down mEPSC amplitude and the number of channels in Mecp2 KO neurons. Intriguingly, TTX scaled-up mEPSC frequency in Mecp2 KO neurons, as observed in WT neurons. These findings demonstrate that both pre and postsynaptic homeostatic synaptic plasticity at excitatory synapses are impaired in Mecp2 KO neurons, providing proof-of-principle that restoring HSP may ameliorate neurological deficits in RTT.

Disclosures: **X. Xu:** None. **L. Pozzo-Miller:** None.

Poster

586. Rett Syndrome

Location: Hall A

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Title: CDKL5 is required for spine maintenance during synaptic plasticity

Authors: *D. LI, C. YANG, Z. XIONG;
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Abstract: The X-linked gene cyclin-dependent kinase-like 5 (CDKL5) is associated with severe neurodevelopmental diseases including Rett-like syndrome and early onset seizure. However, the role of CDKL5 in synaptic plasticity remains unknown. Here we find that CDKL5 is tightly regulated by neuronal activity during synaptic plasticity. In cultured hippocampal neurons, the synaptic level of CDKL5 decreases in NMDA-induced chemical LTD (NMDA-LTD) and increases in glycine-induced chemical LTP (glycine-LTP); meanwhile, the dendritic microtubular accumulations of CDKL5 are enhanced in both forms of the plasticity. The

p150glued subunit of the microtubular dynein-dynactin motor is identified as a CDKL5 protein partner. Co-immunoprecipitation assays show that both the interactions of CDKL5 to postsynaptic PSD-95 and to microtubular p150glued are regulated in NMDA-LTD and glycine-LTP, which are consistent with activity-induced CDKL5 translocations. In addition, shRNA knockdown experiments reveal that CDKL5 is essential for activity-dependent spine maintenance. Together, these evidences suggest a critical role of CDKL5 in connecting activity-dependent cargo-specific vesicular trafficking and PSD-95-mediated spine remodeling, thus to maintain spine stability during synaptic plasticity. Our data not only give a hint to uncover the mechanism of activity-dependent vesicular trafficking in synaptic plasticity, but also provide a molecular basis to understand the pathogenesis of CDKL5-related disorders.

Disclosures: D. Li: None. **C. Yang:** None. **Z. Xiong:** None.

Poster

586. Rett Syndrome

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Topic: C.06. Developmental Disorders

Support: R01-NS065027

R21-HD074418

Title: Consequences of hippocampal hyperactivity in the medial prefrontal cortex of Mecp2 knockout mice, a model of the autism Rett syndrome

Authors: *M. PHILLIPS[1], W. LI[2], L. POZZO-MILLER[2];
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Abstract: The balance between excitation and inhibition (E/I) in the central nervous system is crucial for normal brain function. This balance has been found to be altered in numerous brain regions in mouse models of Rett syndrome, a neurodevelopmental, syndromic autism spectrum disorder caused by mutations in the X-linked Methyl-CpG Binding Protein (MECP2) gene. E/I imbalance results in altered network activity levels, causing them to be either hyper or hypoactive. Here, we describe network activity levels in the hippocampus and anterior medial prefrontal cortex (mPFC) of symptomatic male Mecp2 knockout (KO) mice as compared to age-matched wildtype (WT) littermates. We previously demonstrated that the ventral hippocampus

(vHipp) network is hyperactive in Mecp2 KO mice, with increased spontaneous activity of pyramidal cells and reduced synaptic inhibition (Calfa et al. J Neurophysiol 2011, Hippocampus 2015). Consistently, the number of cFos-positive neurons is higher in all vHipp areas and the dentate gyrus of Mecp2 KO mice. In addition, the intensity of EGR1 (zif268) immunolabeling is higher in areas CA1 and CA3 of Mecp2 KO mice. Simultaneous electrophysiology and voltage-sensitive dye (VSD) imaging in acute brain slices confirmed that the vHipp network is hyperactive, as evidenced by the amplitude and spatiotemporal spread of VSD signals in area CA1 during single excitatory postsynaptic potentials evoked by Schaffer collateral stimulation. In contrast, the spatial spread of VSD signals evoked by layer 5 stimulation is smaller in mPFC slices from Mecp2 KO mice, even though their amplitude were comparable to those observed in WT slice (Bregma 1.5:2.0). Consistent with this hypoactivity of the mPFC network, the number of cFos-positive neurons and EGR1 levels are both lower in the mPFC of Mecp2 KO mice. Current studies are focusing on the influence of the vHipp on the prelimibic and infralimbic regions of the mPFC, testing the hypothesis that increased activity of vHipp long-range projections causes heightened feed-forward inhibition in the mPFC, resulting in the hypoactivation of the mPFC network. Such cortical inhibition may contribute to cognitive impairments and autistic features in RTT individuals.

Disclosures: **M. Phillips:** None. **W. Li:** None. **L. Pozzo-Miller:** None.

Poster

586. Rett Syndrome

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Support: IRSF HeART

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Albero di Greta

Summer Program In Neurobiology

R01-NS065027

R21-HD074418

Title: The balance between excitation and inhibition of cortical GABAergic interneurons is altered in both Mecp2 and Cdkl5 knockout mice

Authors: N. MORELLO[1], R. SCHINA[1], R. PIZZO[1], E. CALCAGNO[1], M. PHILLIPS[2], M. SASSOÈ-POGNETTO[1], L. POZZO-MILLER[2], *M. GIUSTETTO[1];
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Abstract: Rett syndrome (RTT) is an X-linked progressive neurodevelopmental disorder. While most RTT patients show mutations of the methyl-CpG-binding protein 2 (MECP2) gene, recently a variant of RTT syndrome was shown to be associated with mutations in the cyclin-dependent kinase-like 5 (CDKL5). Recent published data showed that conditional mouse mutants where Mecp2 or Cdkl5 were selectively ablated in cortical interneurons (INs) recapitulate many RTT features, indicating that GABA (γ-aminobutyric acid)-releasing cells might be a prominent cellular substrate of the disease. However, how the organization of synaptic connectivity of cortical INs is impacted in RTT is still poorly understood. To shed light on this issue, we used immunofluorescence and confocal microscopy to evaluate the density and localization of both excitatory and inhibitory synapses on cortical INs in male Mecp2 knockout (KO) mice at 4 and 8 weeks of age, corresponding to presymptomatic and symptomatic stages of the pathology. Likewise, excitatory connectivity on cortical INs was studied in adult Cdkl5 KO mice. We found a significant increase of VGlut1-positive puncta on the dendrites of parvalbumin (PV) INs in mutant mice of both ages. In contrast, VGlut1 contacts on the dendrites of calretinin (CR) INs were increased only in symptomatic mutants. Moreover, we found that the density of VGAT-positive inhibitory synapses was significantly reduced on the dendrites of PV INs at both ages. To assess possible functional consequences of this altered synaptic connectivity, we performed voltage-sensitive dye (VSD) imaging in acute slices from the primary somatosensory cortex of symptomatic Mecp2 KO mice. The spatial spread of VSD signals during single excitatory postsynaptic potentials evoked by afferent stimulation was smaller in Mecp2 KO slices, consistent with increased inhibitory drive in the mutant neocortex. The analysis of VGlut1-positive puncta in the cortex of Cdkl5 mutant mice showed an increased density of excitatory terminals targeting the dendrites of both PV+ and CR+ subclasses of INs. Moreover, PV+ INs established an increased density of synapses on the soma of L5 pyramidal neurons. Our data suggest that in both models of RTT, the cortical GABAergic inhibitory system is hyperfunctional due to synaptic modifications that alter the excitation/inhibition balance (E/I), thus supporting the hypothesis that RTT might arise from a deregulated E/I ratio in the cerebral cortex.

Disclosures: **N. Morello:** None. **R. Schina:** None. **R. Pizzo:** None. **E. Calcagno:** None. **M. Phillips:** None. **M. Sassoè-Pognetto:** None. **L. Pozzo-Miller:** None. **M. Giustetto:** None.

Poster

587. Mechanisms of Epilepsy Poster Session

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.07. Epilepsy

Support: ERC 339244-FUSIMAGINE

ANR-10-LABX-24 LABEX WIFI

ANR-10-IDEX-0001-02 PSL

ANR-10-IAIHU-06

Title: Functional ultrasound imaging of spontaneous absence seizure in awake rat

Authors: L.-A. SIEU[1,2], A. BERGEL[1,3], E. TIRAN[4], T. DEFFIEUX[4], M. PERNOT[4], J.-L. GENNISSON[4], A. BONNOT[1], M. TANTER[4], *I. COHEN[1];
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Abstract: Absence epilepsy seizures consist in bilateral spike-and-wave discharges occurring in the thalamocortical circuit. In genetic rat models seizures emerge from the somatosensory cortex. A vascular correlate has been described both by NIRS and fMRI experiments, suggesting that localized and/or anticipatory vascular events coincide with EEG discharges. We sought to reveal these events with improved sensitivity and spatiotemporal resolution, using functional ultrasound imaging (fUS). We scanned through the brain of epileptic rats, to address the heterogeneous alterations in neuro-metabolic coupling during hypersynchronous seizure activity. Spontaneous generalized absence seizures were recorded from bilateral cortical electrodes in Genetic Absence Epilepsy Rats from Strasbourg (GAERS). The ultrasound acquisition sequence consisted in alternating 200ms to generate one compound mfUS image followed with 2.8s of processing. Multiple imaging planes were scanned for 10-15min each. In order to test the effect of the imaging procedure, we quantified both the relative time spent seizing and seizure duration, and found no significant difference between control and imaging conditions. Hemodynamic changes in seizure-associated areas ranged from -10% to +20%. We found distinct patterns of correlation across structures along the antero-posterior axis. Hyper-perfusion in the somatosensory cortex and thalamus was concomitant with hypo-perfusion in the Caudate Putamen and no variation in the hippocampus. Although absence seizures are generalized throughout neocortex, vascular alterations showed spatial compartments, and lateralization in the frontal primary sensory cortex

perfusion was observed in half of the animals. Furthermore, consecutive seizures with a similar bilateral cortical EEG profile could display distinct bilateral or unilateral perfusion course. Comparing the dynamics of cortical and thalamic areas coupled to seizure revealed synchronous oscillations in the perfusion pattern. Thus, the responses we observed across anatomical structures are compatible with EEG-fMRI experiments that found inversed electrographic-hemodynamic coupling between the cortex and CPu, and with time-resolved EEG-NIRS experiments that indicate blood flow fluctuations around seizures initiation. With the best of time and spatial resolution of these two techniques, fUS further points to cortical decoupling between electrographic activity and perfusion, with both static and transient components, in naturally occurring seizures.

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Poster

587. Mechanisms of Epilepsy Poster Session

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Topic: C.07. Epilepsy

Support: the U.S. Army Medical Research and Material Command (grant PR100040)

Title: Archetypal early and late excitability changes during epileptogenesis revealed by sensory evoked and spontaneous field potentials in hippocampus

Authors: *Z. SMITH[1], A. M. BENISON[1], K. M. RODGERS[1], F. M. BERCUM[1], F. E. DUDEK[2], D. S. BARTH[1];
[1]Psychology and Neurosci., Univ. of Colorado Boulder, Boulder, CO; [2]Univ. of Utah, Salt Lake City, UT

Abstract: Acquired epilepsy is characterized by the development of spontaneous recurrent convulsive seizures following a precipitating insult, including traumatic brain injury, *Status Epilepticus*, and Febrile seizures. Initial brain trauma is followed by a highly variable seizure free “latent” period lasting months to years. While this behaviorally silent period is thought to involve progressive neural network changes leading to hyperexcitability, very little is known about the underlying etiology. This study uses a well-established chemoconvulsive animal model of acquired epilepsy combined with 24/7 video EEG recording and an external auditory stimulus to passively monitor and actively probe the hippocampus for changes in excitability. Passive

EEG monitoring indicates increases in pre-Ictal discharges (used diagnostically in epileptic patients) prior to the development of spontaneous seizures. Actively probing the hippocampus demonstrated reproducible, progressive and archetypal alterations in hippocampal excitability that were predictive of the forthcoming epileptic state. Together, these two mechanisms provide for a temporally accurate electrographic biomarker of epilepsy risk that identifies novel phases of epileptogenesis and emerging windows for therapeutic intervention, as well as providing a much needed tool for the understanding of the basic mechanisms underlying acquired epilepsy.

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Poster

587. Mechanisms of Epilepsy Poster Session

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Topic: C.07. Epilepsy

Support: European Union's Seventh Framework Programme (FP7) under grant agreement n°602102 (EPITARGET)

Title: Comparison of F-18-fluorethyltyrosine and F-18-fluordesoxyglucose positron emission tomography in chronically epileptic rats

Authors: *J. P. BANKSTAHL[1], P. BASCUNANA[2], I. LEITER[2,3], F. M. BENGEL[2], M. BANKSTAHL[3];
[2]Nuclear Med., [1]Hannover Med. Sch., Hannover, Germany; [3]Pharmacol., Univ. of Vet. Med., Hannover, Germany

Abstract: Rational In the epileptic focus of patients suffering from chronic epilepsy changes in glucose metabolism are well described and used for pre-surgical diagnostics. Investigation of protein metabolism might add valuable additional information concerning epilepsy-associated brain pathology. In this study, we evaluated positron emission tomography (PET) *in vivo* imaging using a marker for protein metabolism, F-18-fluorethyltyrosine (FET), in comparison to the standard marker for brain energy metabolism, F-18-fluordesoxyglucose (FDG), in chronically epileptic rats. Methods Control animals (n=4) and chronic epileptic animals (lithium-pilocarpine model, n=5) were dynamically PET scanned twice under isoflurane anesthesia after injection of FDG (16.5±1.9 MBq) or FET (19.1±0.5 MBq), respectively, and glucose blood levels were obtained. PET images were analysed by calculating influx rate Ki and metabolic rate

MRglu (Patlak plot for FDG) and volume of distribution Vt (two-compartment model, image-derived input function from arteria carotis for FET) of brain regions obtained by applying a VOI template map to the images (amygdala, piriform cortex, hippocampus, thalamus, cerebellum). Results With FDG, epileptic animals showed generalized reduction in Ki in all analysed brain regions of up to 35% (p=0.001), whereas MRglu was only reduced in hippocampus (25.14±0.24 vs. 21.56±1.00 mmol min-1 100ml-1, p=0.017). FET modelling resulted in a tendency for reduced Vt only in the hippocampus (0.62±0.03 vs. 0.50±0.04 ml cm-3, p=0.065), but not in other investigated brain regions. Correlation analysis between FDG MRglu and FET Vt in the hippocampus revealed a Pearson correlation coefficient r of 0.69 (p=0.041). Conclusion Our data reveal that metabolic underperformance in the epileptic focus is not limited to brain energy metabolism but also present for protein metabolism. This is reflected also by correlation between FDG MRglu and FET Vt values and might serve as an additional marker for pre-surgical evaluation of the epileptic focus.

Disclosures: J.P. Bankstahl: None. **P. Bascunana:** None. **I. Leiter:** None. **F.M. Bengel:** None. **M. Bankstahl:** None.

Poster

587. Mechanisms of Epilepsy Poster Session

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Support: Epilepsy Foundation Predoctoral Research Training Fellowship

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Title: Retrograde tracing reveals changes in monosynaptic inputs onto neonatal- vs. adult-born dentate granule cells in a rodent model of temporal lobe epilepsy

Authors: *X. DU[1,2], H. ZHANG[2], E. WOLF[2], J. PARENT[2,1];
[1]Neurosci. Grad. Program/MSTP, [2]Dept. of Neurol., Univ. of Michigan, Ann Arbor, MI

Abstract: Adult neurogenesis in the hippocampal dentate gyrus (DG) is potentiated by seizures. In rodent temporal lobe epilepsy models, however, dentate granule cell (DGC) neurogenesis is aberrant and adult-born DGCs generated after status epilepticus (SE) develop abnormal connections that are postulated to contribute to pathophysiology. To understand how SE affects

the integration of adult-born DGCs, we use a dual-viral tracing approach to identify and compare inputs onto neonatal- versus adult-born DGCs. A retrovirus (RV-Syn-GTR) driven by the human Synapsin1 promoter and expressing GFP, an avian retroviral receptor (TVA), and the rabies glycoprotein (Rgp) is used to selectively infect dividing cells in the rat DG at either postnatal day (P) 7 or P60 to birthdate either neonatal- or adult-born DGCs, respectively. Rats undergo pilocarpine-induced SE at P56 and then receive bilateral injections of an avian envelope protein (EnvA)-pseudotyped rabies virus, with Rgp replaced by mCherry (RbV-mCh) 10 weeks later. RbV-mCh selectively infects RV-Syn-GTR transduced neurons through EnvA binding to its cognate receptor, TVA. RbV-mCh then complements with Rgp provided by Rv-Syn-GTR and retrogradely crosses synapses, labeling first-order presynaptic neurons with mCh. As traced presynaptic inputs lack Rgp, RbV-mCh cannot spread further. Animals were euthanized 7 d post RbV-mCh injection. Control animals received saline injections rather than pilocarpine. We identify 'starter' DGCs as GFP+/mCh+ and their first-order inputs as mCh+/GFP-. We found mCh+ inputs onto both neonatal and adult-born DGCs from the DG hilus, entorhinal cortex (EC), septum, and supramammillary nucleus (SMN) in both SE and control animals. Surprisingly, we also observed a significant amount of mCh+/GFP- inputs from CA2, CA3, CA1, as well as subiculum in both P7 and P60-injected SE animals. Inputs from these areas were present in both P7 and P60-injected control animals, but to a much lesser degree than in SE animals. Triple-labeling also revealed decreased inhibitory input from parvalbumin (PV)+ and somatostatin (SST)+ interneurons onto adult-born DGCs after SE as compared with controls. Together, these finding suggest that adult-born DGCs receive decreased inhibitory inputs and new inputs from areas that were previously not known to project to the DG. Ongoing experiments are aimed at identifying whether there are changes in inhibitory inputs onto neonatal-born DGCs after SE and also whether excitatory inputs from DGCs and mossy cells onto other DGCs also change after SE.

Disclosures: **X. Du:** None. **H. Zhang:** None. **E. Wolf:** None. **J. Parent:** None.

Poster

587. Mechanisms of Epilepsy Poster Session

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Topic: C.07. Epilepsy

Support: NIH/NINDS 5R01NS060757-06

Title: Identifying propagation and source of epileptiform activity in the hippocampus in transgenic mice with voltage-sensitive fluorescent proteins

Authors: *C.-C. CHIANG[1], L. E. GONZALEZ-REYES[2], R. SHIVACHARAN[2], D. M. DURAND[2];
[1]Biomed. Engin., [2]Case Western Reserve Univ., Cleveland, OH

Abstract: There is increasing interest in propagation and foci identification of epileptiform activity recently. Although the epileptiform activity can be spatially recorded by means of electrode array or voltage-sensitive dye, they are limited to the low spatial resolution or low signal-to-noise ratio. A voltage-sensitive fluorescent protein can provide solutions with higher spatial resolution and sensitivity to low voltage change for observing the epilepiform activity in the larger areas. In this manuscript, we study the propagation and source of the epileptiform activity detected by optical recordings in the hippocampus. We used transgenic mice with a voltage-sensitive fluorescent protein, called VSFP-butterfly 1.2, which enables optical recordings of the pyramidal cells in the hippocampus. The longitudinal hippocampal slices were prepared and epileptiform activity was induced by immersing the slice in the aCSF with 100μM 4-aminopyridine solution. The fluorescent change induced by intrinsic neuronal activity was detected through a fluorescent microscope with emission filters (542 nm and 590 nm) and an excitation filter (483 nm) and a high speed camera was used to acquire image sequence at 100 frame rate. A glass pipette electrode was also used to record local field potential for the comparison. The result shows that the fluorescent change around the glass pipette electrode is related to the field potential and the similar changes were also observed in the whole cellar layers and dendrites regions of the longitudinal hippocampal slice. By analyzing the image sequence, the result shows that the epileptiform activity could propagate through the longitudinal hippocampal slice. The speed of propagation of the epileptiform activity is around 0.05-0.1 m/s which is similar to our previous results detected by electrode array. Furthermore, the source of epileptiform activity could be differentiated from the spike of epileptiform activity and avoid the problem which the source and spike were interfered when using electrode array to record. A source of the epileptiform could be observed during the period of propagation and a very slow change of the source pattern is detected during the period of propagation. In summary, optical imaging could identify the propagation of the epileptiform activity and the change of the source pattern.

Disclosures: C. Chiang: None. **L.E. Gonzalez-Reyes:** None. **R. Shivacharan:** None. **D.M. Durand:** None.

Poster

587. Mechanisms of Epilepsy Poster Session

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Topic: C.07. Epilepsy

Support: Duke University 4410161 and 3912247

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Cure AHC Foundation 3833697

Title: Increased CA1 hippocampal excitability in Na, K-ATPase α3 subunit mutant (D801N) knock-in mice

Authors: *A. S. HUNANYAN[1], A. HELSETH[1], S. ADIL[1], M. LINABARGER[1], E. AREHART[1], L. CHUNG[2], M. MIKATI[1,2];
[1]Pediatrics Neurol., [2]Neurobio., Duke Univ. Med. Ctr., Durham, NC

Abstract: Na, K-ATPase dysfunction involves in many neurological disorders including epilepsy and alternating hemiplegia of childhood (AHC). AHC is a disorder that manifests intermittent hemiplegias, dystonia and epileptic seizures (Mikati et al. 2000). Recently we have developed a knock-in mouse (Mashl+/-) that bears the most common mutation (D801N; mutation in Na/K pump α3 subunit) causing AHC (Hunanyan et al. 2015). Using extracellular recordings from hippocampal CA1 pyramidal cell body layer recently we have found that mutant mice exhibited increased excitability in response to 1Hz repetitive electrical stimulation of Schaffer collateral (Hunanyan et al. 2015). To elucidate the cellular mechanisms of increased hippocampal excitability in this study we performed whole-cell patch clamp recordings from individual CA1 pyramidal cells and compared intrinsic properties of CA1 pyramidal cells in wild-type littermates (WT) and Mashl+/- mice. Sagittal hippocampal slices (300 μm) were prepared from 21-30 day old mice (males and females). CA1 pyramidal cells were identified using upright Zeiss Axioskop microscope with DIC and IR-1000 videocamera. We obtained whole cell recordings in current clump mode (Multiclamp 700B and Axoclamp 2B) using glass microelectrodes (4-6MΩ resistance). Resting membrane potential of Mashl+/- mice CA1 pyramidal cells were significantly depolarized compared with WT littermates (Mashl+/-: -63.5 ± 0.8mV, n = 11mice/41cells vs WT: -59 ± 0.4mV, n = 6mice/36cells; p = 0.001). Rheobase (a minimum current to induce AP) was significantly smaller in Mashl+/- mice (18.3 ± 2.5pA, n=6/32cells) compared with WT littermates (37.5 ± 6.4pA, n = 8/24cells; p = 0.026). There were no significant difference in input resistance (Mashl+/-: 170.3 ± 9.4MΩ, n = 6/21cells vs WT: 149.8 ± 10.2MΩ, n = 8/32cells, p = 0.180), AP amplitude (Mashl+/-: 77 ± 2.1mV, n = 6/32cells vs WT: 76 ± 3mV, n = 8/24cells; p = 0.691), after hyperpolarization amplitude (Mashl+/-: 3.5 ± 0.2mV, n = 6/32cells vs WT: 2.7 ± 0.4mV, n = 8/24cells; p = 0.121) and Sag amplitude (Mashl+/-: 6.2 ± 0.4mV, n = 6/32cells vs WT: 8.3 ± 1.1mV, n = 8/24cells; p = 0.140). We

conclude that depolarized resting membrane potential and decreased rheobase in Mashl+/-mice CA1 pyramidal cells could be one of the causes of increased excitability in Mashl+/- mice hippocampal slices. Currently we are performing voltage clamp experiments to record spontaneous and evoked IPSPCs/EPSCs to find out which neurotransmitter(s) could be involved in increased excitability.

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Poster

587. Mechanisms of Epilepsy Poster Session

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 587.07/F22

Topic: C.07. Epilepsy

Title: Increased sensitivity to chemoconvulsant in Akt3 transgenic mice is improved by RAD001 treatment

Authors: *S. M. MCTIGHE[1], S. J. NEAL[1], A. J. GRAY[1], K. CAPRE[1], S. L. LEGARE[1], D. S. BURDETTE[2], J.-C. DODART[1];
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Abstract: Genetic data indicate that mutations resulting in hyperactivation of the mTOR pathway are associated with brain overgrowth, seizures and autistic-like behaviors. Preliminary clinical data also suggest that Everolimus (RAD001 - mTOR inhibitor) reduces seizure frequency in patients with tuberous sclerosis. AKT is activated upon phosphorylation by mTORC2, and among other downstream effectors is hypothesized to signal through activation of mTORC1 leading to phosphorylation of S6 (P-S6). A mouse model expressing a gain of function mutation in the Akt3 gene has been reported to show reduced seizure threshold by both electroconvulsive treatment (ECT) and on pentylenetetrazol (PTZ; chemoconvulsant) administration. Here we investigate the effects of subchronic RAD001 treatment on seizure severity in this Akt3 transgenic mouse model. Data reported here from a full dose response of PTZ treatment indicate that Akt3 transgenic mice are hypersensitive to acute PTZ treatment as compared to wild-type littermate controls. Subchronic RAD001 dosing (30 mg/kg, PO, BID for 5 days) robustly inhibited the downstream mTOR pathway activity marker, S6 phosphorylation, while also significantly reducing PTZ-induced seizure severity in Akt3 transgenic mice. This

study suggests that the altered seizure threshold in Akt3 transgenic mice may be mediated by hyperactivated mTOR signaling.

Disclosures: **S.M. McTighe:** A. Employment/Salary (full or part-time):; Novartis Institutes for Biomedical Research. **S.J. Neal:** A. Employment/Salary (full or part-time):; Novartis Institutes for Biomedical Research. **A.J. Gray:** A. Employment/Salary (full or part-time):; Novartis Institutes for Biomedical Research. **K. Capre:** A. Employment/Salary (full or part-time):; Novartis Institutes for Biomedical Research. **S.L. Legare:** A. Employment/Salary (full or part-time):; Novartis Institutes for Biomedical Research. **D.S. Burdette:** A. Employment/Salary (full or part-time):; Novartis Institutes for Biomedical Research. **J. Dodart:** A. Employment/Salary (full or part-time):; Novartis Institutes for Biomedical Research.

Poster

587. Mechanisms of Epilepsy Poster Session

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 587.08/F23

Topic: C.07. Epilepsy

Title: Electrophysiological and molecular characterization of a neonatal pilocarpine model

Authors: *C. WORMUTH, C. HENSELER, K. BROICH, M. WEIERGRÄBER, A. PAPAZOGLOU;
Federal Inst. For Drugs and Med. Devices, Bonn, Germany

Abstract: Epilepsy is a neurological disorder that is characterized by involuntary spontaneous seizures. Temporal lobe epilepsy (TLE) is a complex partial epilepsy in which patients experience recurrent epileptic seizures emerging mainly from the hippocampus and amygdala of the uni- and/or bi- lateral temporal lobes of the brain. Bromide is a cheap and easy to use antiepileptic drug (AED) that is administered to children only as a tertiary AED. Interestingly, administration during childhood does not lead to the severe side effects that can be observed in adults. The pilocarpine model is very common in adult rats and induces chronic epileptic seizures in the already consolidated brain. It mimics both the underlying aetiology and symptoms of TLE. This includes: i) seizure foci in the hippocampus; ii) a latent period as a seizure-free time before phenotype manifestation iii) hippocampal sclerosis. In order to investigate the different effect of bromide in adults and children, we developed a neonatal pilocarpine rat model with childhood onset. Epilepsy was induced in rat pups at different ages, with variable treatment durations as well as different pilocarpine and diazepam doses. Based on survival rates and seizures incidents, a protocol was selected for further validation. EEG was recorded 28, 49 and

112 days after treatment in the hippocampal CA1 and motor cortex M1 region for 4-7 days and seizures were analyzed with a Seizure Detection Module (Neuroscore, DSI). Furthermore, literature suggests that voltage activated calcium channels are likely to be predominant candidates for calcium elevation during most epileptiform activity. Therefore, we studied molecular changes in the neonatal epileptic rat hippocampal system using quantitative Real Time PCR analysis. In conclusion, our model is easy to use and yields the desired outcome. Mortality rates are as low as 10-20% while 70-90% of the survival animals present an epileptic phenotype. It presents seizures in the hippocampus and motor cortex on a reproducible manner and proofs the distinct role of voltage-gated calcium channels in epileptogenesis.

Disclosures: C. Wormuth: None. **C. Henseler:** None. **K. Broich:** None. **M. Weiergräber:** None. **A. Papazoglou:** None.

Poster

587. Mechanisms of Epilepsy Poster Session

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Program#/Poster#: 587.09/F24

Topic: C.07. Epilepsy

Support: VHA Research Service

NIH Grant UO1 NS074926

Title: Cholinergic status epilepticus induces widespread brain damage in postnatal day 7 rat pups

Authors: D. TOROLIRA[1], L. SUCHOMELOVA[1], *J. NIQUET[1,2], C. WASTERLAIN[1,2]; [1]Epilepsy Res. Lab., VA Greater Los Angeles Healthcare Syst., Los Angeles, CA; [2]Neurol., UCLA, Los Angeles, CA

Abstract: Status Epilepticus (SE) is common in neonates and infants, and is associated with adverse developmental outcomes. Newborn humans are treated in neonatal ICUs, and many survive with brain damage. However, the role of neonatal SE in this injury is uncertain. Until now, we have lacked an animal model in which seizures induces neuronal injury in rodent models at ages below postnatal day 12 (P12) unless seizures are combined with inflammatory stressors such as lipopolysaccharide (Auvin et al 2007). In this present study, we developed an animal model of SE in P7 rats, which are developmentally close to human neonates. Rat pups were injected ip with high dose lithium (5 mEq/kg) on post-natal day 6, and the next morning with very high dose pilocarpine (320 mg/kg), plus methylscopolamine to reduce secretions (1

mg/kg). This model was designed to mimic the seizures induced by 1.6/2 x LD50 of soman in adult rats (Tetz et al, 2006), and was adapted by us for use in P7 pups. Pups were kept in a special warming chamber to maintain their normal temperature (34-35°C). EEGs were recorded in selected animals and showed continuous seizures for 59.4 ± 6.3 min. O_2 saturation was measured non-invasively from tail probes in selected animals, and our results showed no significant hypoxemia. A third group of animals was perfused with 4% phosphate-buffered paraformaldehyde 6 or 24 hrs after SE. We examined the severity of neuronal injury on coronal sections using fluoro-jade B (FJB) and an antibody against caspase-3. A few FJB stained cells were found in the hippocampal formation and in extrahippocampal structures of sham control pups. Six hrs after SE onset, neuronal injury (FJB staining) was significantly different from controls in neocortex, thalamus, dorsal CA3 and dorsal dentate gyrus. Twenty-four hrs after SE onset, significant neuronal injury was observed in CA1/subiculum, CA3, dentate gyrus, thalamus, neocortex, amygdala, piriform cortex, lateral entorhinal cortex, hypothalamus, caudate putamen, globus pallidus, ventral pallidum, nucleus accumbens. At 24 hrs post-SE, caspase-3a IR was significantly increased in CA1/subiculum, thalamus, and neocortex compared to sham. These caspase-3a-IR neurons have distinct changes such as fragmented nuclei, suggesting that SE triggered an irreversible form of cell injury. In conclusion, we have developed a model of cholinergic SE in P7 rat pups, which combines high survival (70% survival at 24hrs) and widespread brain injury. These studies show that the immature brain is vulnerable to severe forms of SE.

Disclosures: **D. Torolira:** None. **L. Suchomelova:** None. **J. Niquet:** None. **C. Wasterlain:** None.

Poster

587. Mechanisms of Epilepsy Poster Session

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Program#/Poster#: 587.10/F25

Topic: C.07. Epilepsy

Support: Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT and Future Planning (#NRF-2013R1A1A2060894 and #NRF-2013R1A1A1007378), Republic of Korea

TTH Tu, Y Nam, and HQ Tran are involved in BK21 PLUS program, National Research Foundation of Korea

Title: Pharmacological and genetic inhibition of protein kinase Cδ alleviates hippocampal neurodegeneration induced by trimethyltin

Authors: T.-H. T. TU[1], Y. NAM[1], H.-Q. TRAN[1], J. JEONG[2], *E.-J. SHIN[1], H.-C. KIM[1]; [1]Col. of Pharmacy, Kangwon Natl. Univ., Chunchon, Korea, Republic of; [2]Col. of Medicine, Chung-Ang Univ., Seoul, Korea, Republic of

Abstract: We investigated whether protein kinase C (PKC) is involved in trimethyltin (TMT)-induced neurotoxicity. Treatment with TMT resulted in a significant increase of PKCδ out of PKC isozymes (i.e., α, βI, βII, δ, and ζ) in the hippocampus of wild-type (WT) mice. Consistently, treatment with TMT resulted in significant increases in cleaved PKCδ expression. Genetic or pharmacological inhibition (PKCδ knockout or rottlerin) was less susceptible to TMT-induced seizures than WT mice. TMT treatment increased glutathione oxidation, lipid peroxidation, protein oxidation, and levels of reactive oxygen species. These effects were more pronounced in the WT mice than in PKCδ knockout mice. In addition, the ability of TMT to induce nuclear translocation of Nrf2, Nrf2 DNA binding activity and upregulation of γ-glutamyl cysteine ligase was significantly increased in the PKCδ knockout mice and rottlerin-treated WT mice. Furthermore, neuronal degeneration (as shown by nuclear chromatin clumping and TUNEL-staining) in WT mice was most pronounced 2 d after TMT. At the same time, TMT-induced inhibition of phosphoinositol 3-kinase (PI3K)/Akt signaling was evident, thereby decreasing phospho-Bad, expression of Bcl-xL and Bcl-2, and the interaction between phospho-Bad and 14-3-3 protein, and increasing Bax expression and caspase-3 cleavage were observed. Rottlerin or PKCδ knockout significantly protected these changes in anti- and pro-apoptotic factors. Importantly, the protective effects (i.e., Nrf-2-dependent glutathione induction and pro-survival phenomenon) of rottlerin were counteracted by the PI3K inhibitor LY294002. Therefore, our results suggest that down-regulation of PKCδ and up-regulations of Nrf2-dependent glutathione defense mechanism and PI3K/Akt signaling are critical for attenuating TMT neurotoxicity.

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Poster

587. Mechanisms of Epilepsy Poster Session

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 587.11/F26

Topic: C.07. Epilepsy

Title: Evoked lateral amygdala neuron activity in rats with acquired sound-induced seizures

Authors: H. K. ANDERSEN, D. M. GIANGRASSO, A. J. ROSSI, K. L. PATTERSON, D. E. COBB, *M. C. ZRULL;
Psychol, Appalachian State Univ., Boone, NC

Abstract: In reflex epilepsy, an inherited or acquired progressive disorder, an external stimulus evokes abnormal neural activity that can include generalized convulsive seizures. Rodent models feature a neural network that processes sound abnormally and promotes audiogenic seizures (AGS); most research on the network and its physiology is based in genetically epilepsy prone rats (GEPRs). For AGS in GEPRs, abnormal neural activity begins in the midbrain and spreads to the forebrain via the lateral amygdala (LA). Long-Evans rats are resistant but can be primed for AGS, and it is assumed that the same neural network supporting AGS in GEPRs mediates seizures in these rats with acquired reflex epilepsy. We examined seizure-induced neural activity in the LA and basolateral amygdala (BLA) of rats with acquired AGS using the activity marker c-fos. On postnatal day (pnd) 18, Long-Evans rats (n=12) were primed for AGS (120 dB, 10 kHz pips, 8 min). Age-matched rats (n=12) served as controls. Primed rats were tested for AGS susceptibility (120 dB noise) between pnd 32 and 62. On pnd 32 after an AGS induction for primed rats, 4 AGS and 4 control rats spent 60 min in the quiet and dark to allow expression of c-fos protein and were then sacrificed. Brain tissue was processed for c-fos immunohistochemistry. The protocol was repeated on pnd 46 for 4 more primed rats after a 6th sixth AGS induction and 4 more age-matched controls and on pnd 62 after the 12th AGS induction for the last 4 primed rats and 4 controls. Counts of c-fos positive neurons were made for LA and BLA across the groups using a digital camera, light microscope, and stereological techniques. For LA, a single AGS produced no more evoked activity than seen in control brains; however, on pnd 46 after 6 inductions, LA in the AGS brain exhibited nearly 1000% more c-fos positive neurons than in control LA ($p<.01$). On pnd 62, after 12 AGSs for primed rats, the LA contained 794% more activated neurons than in age-matched controls ($p<.01$). Within primed rats, the increase in LA neural activation from 1 to 6 or 12 inductions was 343% ($p<.01$). Fos-positive neuron counts from sampling frames in BLA were minimal for both primed rats after 1, 6 or 12 inductions and age-matched controls. On average, counts of activated neurons ranged from 1.0 (SD=1.1) to 2.4 (SD=1.7) for AGS brains and averaged 1.0 (SD=0.5) for controls across pnd 32, 46 and 62 cohorts. The data suggest neural activity allowing sound-induced seizures to generalize in primed and GEPR models of reflex epilepsy is the same, at least in terms of the role of LA as an important relay nucleus from brain stem to forebrain structures, reinforcing the likelihood of similar networks for acquired and inherited AGS in rat.

Disclosures: H.K. Andersen: None. **D.M. Giangrasso:** None. **A.J. Rossi:** None. **K.L. Patterson:** None. **D.E. Cobb:** None. **M.C. Zrull:** None.

Poster

587. Mechanisms of Epilepsy Poster Session

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Topic: C.07. Epilepsy

Support: Dr. Ralph and Marian Falk Medical Research Trust

Title: Failure of synaptic transmission may contribute to seizure propagation

Authors: *A. BHANSALI, W. VAN DRONGELEN, A. K. TRYBA;
Univ. of Chicago, Chicago, IL

Abstract: Epilepsy is one of the most prevalent neurological diseases, affecting about 1% of the world population, but the mechanisms underlying seizure initiation, propagation and termination are not well understood. For neurons embedded in an active network, it is generally assumed that there are straightforward linear or sigmoidal relationships between net synaptic input and neuronal firing. However, due to the extreme conditions during a seizure, such a straightforward input-output relationship may vanish. For example, a paroxysmal depolarization shift (PDS) can occur, in which a neuron undergoes high-amplitude suprathreshold synaptic depolarization while it fails to generate action potentials. The PDS burst, a cellular hallmark of epilepsy, represents a neuronal activity-driven depolarization block that affects transmission within the network and may contribute to counterintuitive emergent behavior during seizures. In order to investigate the effect of PDS bursts on synaptic transmission, we performed whole-cell patch-clamp recordings of synaptically coupled rat hippocampal neurons in dissociated culture. Depolarizing current injections were used to determine the minimal amount of current required to induce action potential firing or a PDS-like burst. Current clamp (n=8) and voltage clamp measurements (n=3) revealed that PDS depolarization block led to failure of synaptic transmission in both inhibitory (n=2) and excitatory (n=8) neurons. Importantly, the amount of current needed to evoke a PDS-like burst was ~40% less in inhibitory than excitatory neurons, which suggests that inhibitory neurons enter depolarization block more readily than excitatory neurons. At the cellular level, our studies demonstrate that PDS depolarization block can create a counterintuitive relationship, such that MORE excitatory input generates LESS synaptic output. In addition, PDS bursts can lead to failure of inhibitory synaptic transmission before excitatory output is affected, which may explain the collapse of inhibitory signaling that precedes seizure propagation, an observation that supports our group's recent modeling work (Meijer et al., 2015).

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Poster

587. Mechanisms of Epilepsy Poster Session

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Program#/Poster#: 587.13/F28

Topic: C.07. Epilepsy

Title: Online measurement of glutamate levels during pentylenetetrazole-induced epileptiform activity using a high temporal resolution technique and simultaneous EEG recording

Authors: *K. PARDO, A. MORALES-VILLAGRÁN, L. MEDINA-CEJA;
Univ. de Guadalajara, Guadalajara, Mexico

Abstract: Online measurement of glutamate levels during pentylenetetrazole-induced epileptiform activity using a high temporal resolution technique and simultaneous EEG recording Pardo-Peña Kenia*, Morales-Villagrán Alberto and Medina-Ceja Laura Laboratory of Neurophysiology and Neurochemistry. Department of Molecular and Cellular Biology, CUCBA, University of Guadalajara, Jalisco, México. The study of neurotransmitters could describe the mechanisms and the progression of neurological diseases. Dynamic measurement of glutamate concentration is valuable for understanding neuronal communication under physiological and pathological conditions such as epilepsy. Microdialysis is a popular method for such measurements, but its use is hampered by its considerably slow temporal resolution in comparison with many dynamic processes in the CNS, with time sample collection varying from 1 to 30 min. In this study, a new approach is presented for measuring the recovery and quantification of glutamate during epileptiform activity every 200 ms. This method consist on mixing hippocampus microdialysate with an enzymatic reactor composed by glutamate oxidase, and Amplex Red which in presence of horse radish peroxidase generates a derivate (resorufin) that fluoresces at 590 nm when excited at 560 nm. Excitation was induced with a laser beam and the fluorescence intensity was determined with a CCD detector, the signal intensity was proportional to the glutamate concentration. We applied this novel technique to relate glutamate level with epileptiform activity induced by PTZ (75mg/kg, i.p) using a deep microelectrode implanted in hippocampus. The basal concentration of glutamate was 7.1±0.42 μM, detected before PTZ injection. The data showed an increase in glutamate level of 15.83 μM (122%) during the first seizure induced by PTZ, the latency to first epileptiform discharge was 2.5±0.35 minutes after injection, however glutamate concentrations increased even more when epileptiform activity was constant, reaching a value of 24.37 μM (243%) and this increase remained high throughout seizures before the death of animals. In contrast, glutamate levels observed after infusing a high potassium solution was 8.63 μM that represents a small increase of 21%. With respect to electrical activity frequency remained without significant changes in any period (2 Hz) but with significant changes in amplitude during seizures (452% compared with

baseline before PTZ injection). These data support the use of this novel technique for neurochemical studies *in vivo* to obtaining more specific information with high temporal resolution on mechanisms that occur in pathological conditions.

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Poster

587. Mechanisms of Epilepsy Poster Session

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Topic: C.07. Epilepsy

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Title: Interleukin-1β augments neuronal cell death induced by status epilepticus in the developing dentate gyrus by a mechanism independent of IL-1RI activation

Authors: *L. LOPEZ-MERAZ[1], J.-S. MEDEL-MATUS[2], C. RINCÓN-LÓPEZ[3], A. TLAPA-PALE[3], L. BELTRÁN-PARRAZAL[1], C. PÉREZ-ESTUDILLO[1], C. MORGADO-VALLE[1]; [1]CICE, UNIVERSIDAD VERACRUZANA, XALAPA, Mexico; [2]Dept. of Pediatrics, Neurol. Div., UCLA, Los Angeles, CA; [3]Facultad de Química Farmaceútica Biológica, UV, Xalapa, Mexico

Abstract: Interleukin-1beta (IL-1β) has been associated with neuronal cell death induced by acute seizures in the mature and developing brain. However, the role of this inflammatory cytokine on neuronal cell death induced by status epilepticus (SE) in the immature hippocampus is still under study. The goal of this research was to analyze the participation of IL-1β and its receptor IL-1RI on the dentate gyrus (DG) neuronal cell death induced by SE in fourteen days-old (P14) rat pups. Pups (both sex) were given 3 mEq/Kg lithium chloride i.p. on the day before the induction of SE, which was carried out at P14 by subcutaneous injection of 100 mg/Kg pilocarpine hydrochloride. Six h after SE, IL-1β was injected in the right ventricle at different concentrations [0 (vehicle), 0.3, 3, 30 and 300 (n=6 per group) ng/µl]; other experimental groups were injected with the IL-1β receptor natural antagonist IL-1Ra (30 ng/µl) alone or in combination with IL-1β (3 ng/µl) (n=6 per group). Neuronal cell death was evaluated by hematoxylin and eosin staining 24 h post-SE. Data were analyzed by a one-way ANOVA for independent groups followed by a Tukey test. Results showed a significant increase in the number of cells with eosinophilic cytoplasm and fragmented nuclei (suggestive of apoptotic morphology) in the DG granule cell layer ipsilateral to the injection of 3 ng/µl (72.5±10.7) and

300 ng/µl of IL-1β (69 ±9.8), as well as contralateral to the injection of 3 ng/µl (65.9±9.5), when compared to the vehicle group (26.2±3.2, $p<0.05$ and 24.7±3.6, $p<0.05$, respectively); IL-1Ra did not avoid the effect of IL-1β on neuronal cell death ($p>0.05$). Our findings suggest that IL-1β increases neuronal cell death caused by SE in DG granule cell layer by a mechanism independent of IL-1RI activation.

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Poster

587. Mechanisms of Epilepsy Poster Session

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Program#/Poster#: 587.15/F30

Topic: C.07. Epilepsy

Support: Fapesp/2013/08635-5

Title: RNAseq based microRNA and transcriptome profiles of the rat hippocampus subfields

Authors: *A. MATOS[1], A. S. VIEIRA[1], A. M. CANTO[1], K. BRUMATTI[1], C. C. ROCHA[1], B. CARVALHO[1], V. PASCOAL[2], R. GLIOLI[1], I. LOPES-CENDES[1];
[1]Univ. of Campinas, Campinas, Brazil; [2]Fluminense Federal Univ., Nova Friburgo, Brazil

Abstract: Gene expression can be regulated by microRNAs and they are important in many key biological functions. It has been demonstrated that different microRNAs may have different expression pattern in different brain regions. The hippocampus is functionally highly heterogeneous and it is likely to present different pattern of gene expression in different subfields. RNAseq-based transcriptome analyzes offers the possibility of accurate profiling global gene expression. The aim of this study was to analyze and correlate microRNA and transcriptome profiles in different regions of the hippocampus: Dentate Gyrus (DG), CA1, CA2 and CA3 subfields. Five male Wistar rats were euthanized and the brains were processed for laser microdissection using Zeiss PALM LCM. DG, CA1, CA2 and CA3 were collected from each rat, total RNA was extracted, and libraries were prepared for total RNA and small-RNA sequencing in an Illumina Hiseq platform. Sequences were aligned and quantified with the TopHat/DESeq2 pipeline for total RNA and bowtie/DESeq2 for smallRNA. Gene Onthologies, molecular networks and gene interactions were analyzed with the MetaCore® software. The miRNA target was analyzed by miRWalk® software. A total of 63 miRNAs and 4693 genes

were found to be differentially expressed ($p<0,05$) when comparing CA1 with DG. In CA2, 131 miRNAs and 5819 genes were differentially expressed in comparison with DG. In CA3, 96 miRNAs and 6331 genes were found to be differently expressed. Furthermore, when comparing CA2 to CA1, 54 miRNAs and 2645 genes were differentially expressed; CA3 to CA1, 48 miRNAs and 4096 genes were differentially expressed; and CA3 to CA2, 38 miRNAs and 1744 genes were differentially expressed. Enriched gene ontology categories identified miRNAs involved in p53 signaling, immune response IL-10 signaling pathway, microRNA-dependent inhibition of epithelial to mesenchymal transition. For transcriptome data, gene ontology categories identified networks involved in receptor-mediated axon growth repulsion, epidermal growth factor receptor signaling pathway, synaptic vesicle fusion and recycling in nerve terminals. Overall, the most activated genes were regulated by miR- 204, 205, 652, 187, 204, 532-3p, 873, 652, 34b and 375. These miRNAs were significantly down-regulated in our miRNAseq analysis. The present data indicates a large spatial heterogeneity in gene and microRNA expression in the rat hippocampus subfields. A better understanding of such variability may improve our interpretation of the molecular mechanisms involved in normal and pathological conditions related to the hippocampus, such as epilepsy and Alzheimer´s disease.
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Poster

587. Mechanisms of Epilepsy Poster Session

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Topic: C.07. Epilepsy

Support: 5R01DA01314

5R01NS43095

Title: Role of adult neurogenesis in the generation of ectopic neurons in the dentate gyrus and their role in epileptogenesis

Authors: ***A. BELMADANI**[1], D. REN[2], R. J. MILLER[3];
[1]Dept Molec Pharmacol & Biolog Chem, Northwestern Univ., Chicago, IL; [2]Phamacology, [3]Northwestern Univ. Chicago, Chicago, IL

Abstract: Ectopic placement of granule cells (EGCs) in the dentate gyrus (DG) of the hippocampus is a commonly observed feature in epilepsy and some psychiatric diseases. EGCs may cause aberrant network excitability in the dentate gyrus, an important step in the process of epileptogenesis. While most research on adult hippocampal neurogenesis has focused on the sub-granular zone (SGZ) as the local neurogenic source for EGCs, we suggest that the sub-hippocampal zone (SHZ), a region of the dorsal surface of the adult hippocampus, may also be important. Specifically, we showed that SHZ cells display properties of neural stem cells, including expression of the chemokine receptor CXCR4, GABA (A) currents and neurosphere formation when cultured ex-vivo. These cells migrate to the hippocampus along a unique migratory stream (CMS) involving the meninges which express the CXCR4 ligand SDF-1/CXCL12 and can contribute to restoration of the DG and SGZ morphology following their destruction by inflammation. We further showed that upon deletion of CXCR4, some of these cells prematurely differentiate into ectopic neurons in the DG. Our observations indicate that the SHZ is a neurogenic zone in adult mice through migration of NSCs in the CMS. Regulation of CXCR4 signaling in these cells may be involved in repair of the DG and may also give rise to ectopic granule cells in the DG in the context of neuropathology. In keeping with this hypothesis, using a model of epilepsy induced by intrahippocampal injection of kainate, we observed significant changes in CXCR4/SDF-1 signaling accompanied by strong migration of SHZ cells towards the DG, where some became ectopically placed in the hilus and expressed markers for granule neurons. Further investigation of the role of these neurons in the generation of epileptiform activity may identify new therapeutic targets for the control of epileptogenesis

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Poster

587. Mechanisms of Epilepsy Poster Session

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Title: Serial preclinical C-11-PK11195-PET imaging reveals the time course of microglia activation during insult-induced epileptogenesis

Authors: *M. BRACKHAN[1], P. BASCUÑANA[1], F. TWELE[2], F. M. BENGEL[1], M. BANKSTAHL[2], J. P. BANKSTAHL[1];
[1]Nuclear Med., Hannover Med. Sch., Hannover, Germany; [2]Dept. of Pharmacology, Toxicology and Pharm., Univ. of Vet. Med., Hannover, Germany

Abstract: Objective: Accumulating evidence suggests that brain inflammation, triggered by epileptogenic injuries, may contribute to seizure development. Non-invasive nuclear imaging of brain inflammation in animal models of epileptogenesis may identify inflammatory processes as predictive biomarkers that hold potential for translation into the clinic. In this study, we investigated microglia activation indicative of neuroinflammation using C-11-PK11195-PET and immunohistochemical analysis. Methods: As epileptogenic insult, a status epilepticus (SE) was induced in rats by lithium-pilocarpine and interrupted after 90 min by diazepam. Rats (n=4-8 per time point) were subjected to 60 min PET scans followed by a CT for co-registration before SE, directly after SE interruption, 1, 2, 5, 7, 14 , and 22 days, and 14-16 weeks post SE. For data evaluation, brain regions (thalamus, hippocampus, amygdala, entorhinal cortex, cerebellum) were outlined by co-registration with a standard rat brain atlas, and % injected dose/cc and binding potential (simplified reference tissue model) were calculated. For immunohistochemical evaluation, additional rats were decapitated without and 48 hours, 5 or 14 days post SE. Brain sections were stained for CD11b, GFAP, and NeuN and analyzed semi-quantitatively. Results: Following SE, increases in C-11-PK11195 uptake and binding potential (BPnd) occurred in epileptogenesis-associated brain regions, but not in the cerebellum, first appearing 48 hours after SE and peaking between 7 and 14 days after SE (up to 2.09-fold increase in uptake, $p < 0.001$). Uptake and binding potential remained above baseline values up to 3 weeks after SE and were subsequently decreasing until at least 14-16 weeks after SE. Immunohistochemical evaluation revealed microglia and astroglia activation as well as neuronal cell loss in epileptogenesis-associated brain regions at all investigated time points. The time profile of microglia activation corresponded to that demonstrated by C-11-PK11195-PET. Conclusion: The revealed peak in neuroinflammation 1-2 weeks after epileptogenic brain insult enables improved timing of inflammation-targeting antiepileptogenic pharmacotherapy.

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Poster

587. Mechanisms of Epilepsy Poster Session

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Program#/Poster#: 587.18/F33

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Evoked population spike of *in vitro* rat hippocampal brain slice assay for assessment of proconvulsant liability of mGluRs ligands

Authors: *J. ZHAI, A. LAGRUTTA, H. ZENG, Y.-Y. ZHOU, F. SANNAJUST;
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Abstract: Glutamate is a major excitatory neurotransmitter widely distributed in the CNS and modulates the synaptic response via activation of ionotropic and metabotropic glutamate receptors (mGLuRs). Activation of mGluR1 & 5 (group I) and inhibition of mGluR2 & 3 (group II) or some of mGluR4, 6, 7, and 8 (group III) as well as some positive allosteric modulator (PAM) of mGluRs have been shown to induce seizures in animal models following i.c.v. administration, in genetically seizure-prone rats, and or by analysis of spontaneous ictal discharges *in vitro*. Having previously demonstrated the utility of an *in vitro* assay measuring evoked population spikes (PS) in rat hippocampal brain slices to detect seizure liability of ~20 receptor ligands, we explore if the assay can detect the seizurogenic activity of diverse mGluRs ligands associated with epileptic seizures in animals. Ligands including group I mGluRs agonists and group II and III mGluRs antagonists were investigated. PS was electrically evoked at 30-s intervals from Schaffer collateral synaptic pathway and recorded in the cell soma of CA1 pyramidal neurons in brain slices prepared from adult Wistar rats. PS area and PS number were quantified to observe changes in PS morphology by the tested ligands at selected concentrations correlated with *in vivo* studies. DHPG concentration-dependently enhanced both PS number and PS area. The effect was reversed by antagonist DL-AP3. Consistently, (S)-3-HPG and CHPG, selective agonists of mGluR1 and mGluR5, respectively, significantly increased evoked PS like DHPG. Ro 01-6128 and VU 29, PAM of mGluR1 and mGluR5, respectively, could not increase either PS area and or PS number. Surprisingly, LY341495, mGluR2 & 3 antagonist, had no effect on PS at nanomolar concentrations (0.01-1 μM), but increased the PS at micromolar concentrations (3-30 μM). Highly selective group II antagonists, Eglu and APICA at 10-300 μM, could not induce seizures-like multiple PS, suggesting that seizure liability of LY341495 at high concentrations might not result from blockade of group II mGluRs. Finally, either PS area and/or PS number were increased by MSOP and MPPG, group III antagonists, respectively. In conclusion, this *in vitro* rat hippocampal brain slice assay can recapitulate seizure risk liability of majority of mGluRs ligands detected by *in vivo* rodent models. The absence of seizures-like activity from some of mGluR2 & 3 ligands or PAM could be related to the limited distribution of specific receptor subtypes within the CA1 neuronal pathways, or absence of active metabolite(s) as compared to *in vivo* experimental conditions.

Disclosures: J. Zhai: None. **A. Lagrutta:** None. **H. Zeng:** None. **Y. Zhou:** None. **F. Sannajust:** None.

Poster

587. Mechanisms of Epilepsy Poster Session

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Topic: B.07. Synaptic Transmission

Support: American Academy of Neurology, the American Brain Foundation and Beyond Batten Disease Foundation

NIH 5R01NS74772-04

NIH 5R01NS40109-14

Title: Neocortical organotypic slices show spontaneous epileptiform activity and a developmental decrease in neuronal Cl^- concentration

Authors: *J. C. GLYKYS, K. STALEY;
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Abstract: Neocortical acute slices show a progressive decrease in neuronal intracellular Cl^- concentration ($[Cl^-]_i$) during early development. However, some neurons with high $[Cl^-]_i$ could result from slicing trauma in this model. The murine hippocampal organotypic slice develops spontaneous seizure activity after a few days *in vitro,* yet it is unknown if this happens in neocortical organotypic slices. Thus, we aimed to develop a neocortical organotypic slice to study if spontaneous epileptiform activity also occurs in this preparation, if there is a developmental decrease in $[Cl^-]_i$ and if diazepam's effect is correlated with the neuronal $[Cl^-]_i$. We addressed these questions with field potential recordings to study epileptiform activity, and with multi-photon imaging of Cl^-, to study neuronal $[Cl^-]_i$, in neocortical organotypic slices from wild type and transgenic mice expressing a Cl-sensitive fluorophore (Clomeleon). We found: 1) neocortical organotypic slices at days *in vitro* 5 (DIV5) have spontaneous epileptiform activity and the duration of the events decrease with development. 2) There is a progressive decrease in $[Cl^-]_i$ during development, similar to the acute neocortical slice. 3) Diazepam was ineffective in decreasing epileptiform activity at DIV5-6, but effective at DIV9-10 and DIV15. Interestingly, at DIV5-6, diazepam worsened epileptiform activity in 50% of the slices. We conclude that neocortical organotypic slices are a good model to study spontaneous epileptiform activity and that there is a decrease in $[Cl^-]_i$ during early development, not associated with slicing trauma. Finally, diazepam effectiveness is correlated with neuronal $[Cl^-]_i$, which can worsen epileptiform activity during very early development in 50% of the cases (when $[Cl^-]_i$ is high). These results

can explain the reported induction of epileptic activity such as myoclonus by benzodiazepines in some human neonates.

Disclosures: **J.C. Glykys:** None. **K. Staley:** None.

Poster

587. Mechanisms of Epilepsy Poster Session

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 587.20/F35

Topic: C.07. Epilepsy

Title: Alterations of neurovascular coupling in rats with focal epilepsy

Authors: ***Y. SONG**[1], S. GARCIA[1], Y. FROMETA[1], R. A. TORRES[1], J. BAE[1], A. DESHMUKH[1], W.-C. LIN[1], Y. ZHENG[2], J. J. RIERA[1];
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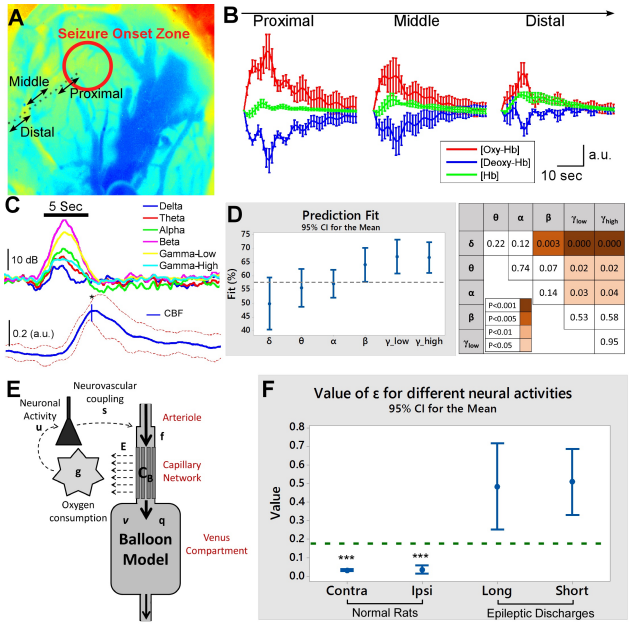
Abstract: Neurovascular couplings (NVCs) in epilepsy have been investigated on preclinical models with either acute or chronic seizures. However, these studies failed to quantitatively verify whether dysfunctions of NVCs exist in epileptic cortex. The answer to this question could have tremendous impacts on the interpretations of neuroimaging data applied in clinical practice, which could result in improving the surgical outcome. In this study, a metabolic-coupled balloon model was employed to study the NVCs both in epileptic (n=4) and normal (n=5) Wistar rats. Chronic epilepsy model was established following a “double-hit” protocol. Spontaneous seizure activities were observed during the intracranial recordings of these epileptic rats, and used as neuronal events in the subsequent analysis. Forepaw stimulation was conducted on normal rats as control. A 16-channel microelectrode array was inserted in corresponding cortical areas to record local field potentials (LFPs). Cerebral blood flow (CBF) was monitored by the laser Doppler flowmetry. In addition, intrinsic optical imaging (IOI) was performed in combination with LFP recordings. Modified Beer-Lambert law was applied on the IOI data to estimate the cerebral blood volume (CBV) and relative deoxy-hemoglobin concentration ([dHb]). LFP, CBF and [dHb] were included in the model to estimate parameters that quantify the relationships between the neuronal activity and the hemodynamic responses: 1) ε is the parameter links the neuronal activity to the CBF response; 2) κ uncovers the relationship between the neuronal activity and [dHb]. Significant increases in CBF were found to be associated with epileptogenesis and forepaw stimulation. Reflections of such neuronal activity within the optical field of view usually resembled an increase of CBV and a decrease of [dHb] with an epicentric origin followed by a

peripheral propagation (Fig A-B). However, parameter ε during epileptic activity and forepaw stimulation were significantly different (P<0.001) (Fig F), which indicated an alteration in NVC exists in epilepsy.



Disclosures: **Y. Song:** None. **S. Garcia:** None. **Y. Frometa:** None. **R.A. Torres:** None. **J. Bae:** None. **A. Deshmukh:** None. **W. Lin:** None. **Y. Zheng:** None. **J.J. Riera:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

Location: Hall A

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NIMH-RO1DA034178 (SM)

NIH T32 Postdoctoral Fellowship (TS)

Epilepsy Foundation Postdoctoral Fellowship (TS)

Title: Dentate gyrus-CA1 hippocampal interneuron desynchronization in chronically epileptic mice running on a virtual linear track

Authors: ***T. SHUMAN**[1], M. JAVAHERIAN[1], C. C. KABA[1], D. J. CAI[1], K. CHENG[1], R. MANAVI[1], N. RAO[1], J. DANESHRAD[1], A. A. FARIBORZI[1], J. LOU[1], S. E. FLORES[1], C. YANG[1], S. GHIAEE[1], M. STRAHMAN[1,2], K. I. BAKHURIN[1], S. C. MASMANIDIS[1], P. GOLSHANI[1];
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Abstract: Interneurons in the hippocampus gate the processing and flow of information through the trisynaptic and temporoammonic pathways. Because there is dramatic reorganization of GABAergic interneuron connectivity in epilepsy, we hypothesized that this is likely to cause profound deficits in hippocampal interneuron synchronization to ongoing theta and gamma oscillations in epileptic mice. To test this hypothesis we used high density silicon probes with 128 recording sites to simultaneously record single units and local field potentials throughout dorsal CA1 and dentate gyrus in head-fixed mice running through a virtual linear track. Pilocarpine-treated epileptic animals showed reduced gamma power in dentate gyrus as well as reduced theta and gamma coherence between CA1 and dentate gyrus indicating reduced synchronization between these regions. We also found a reduction in theta-gamma cross-frequency coupling in epileptic animals. We further examined this synchronization deficit by examining the phase-locking of dentate gyrus interneurons to ongoing theta oscillations and found that while the magnitude of phase-locked firing in individual dentate gyrus interneurons was comparable to control animals, the preferred phase of these cells as a group was more dispersed and shifted to a later phase of theta. Together, these findings indicate a clear desynchronization between dentate gyrus and CA1 regions of the hippocampus of epileptic mice. These changes may contribute to cognitive deficits in chronic epilepsy. Future studies will gauge the efficacy of interneuron replacement therapies on restoring synchrony in dentate gyrus and CA1.

Disclosures: **T. Shuman:** None. **M. Javaherian:** None. **C.C. Kaba:** None. **D.J. Cai:** None. **K. Cheng:** None. **R. Manavi:** None. **N. Rao:** None. **J. Daneshrad:** None. **A.A. Fariborzi:** None. **J. Lou:** None. **S.E. Flores:** None. **C. Yang:** None. **S. Ghiaee:** None. **M. Strahman:** None. **K.I. Bakhurin:** None. **S.C. Masmanidis:** None. **P. Golshani:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

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Support: CNPq Grant 302528/2011-3

PIBIC/Mackenzie

Title: Early life seizures in rodents can disrupt the preference for social novelty unrelated to increased emotionality

Authors: *R. M. CYSNEIROS, I. S. LEITE, A. S. S. CASTELHANO;
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Abstract: We previously demonstrated that male rats subjected to neonatal status epilepticus (SE) displayed social play impairment, deficit in social discrimination, anxiety like behavior and stereotyped behavior with no changes in motor activity. Taking into account the bi-directional relationship between social interaction impairment and the degree of anxiety, this study aimed to evaluate whether the reduction of state of anxiety could minimize the impaired social interaction. Male Wistar rats (PN9) were subjected to SE by pilocarpine administration (380mg/kg) and the controls received saline. Each group received saline or diazepam (1mg/kg) before each behavioral testing. Behavioral tests started from 60 days of postnatal life. The data was analyzed by Mixer Anova using condition (object x unfamiliar rat or familiar rat versus social novelty) as within-subjects factor and groups (EXP versus CTR) and treatment (saline x diazepam) as between-subjects factors. In the social approach phase, both groups spent more time in the compartment with unfamiliar rat as compared with the one with object ($F(1,48) =61,52$; $P=0,000$), but no effect was noted neither for groups ($F (1,48) = 1,075$, $P = 0,305$), treatment ($F(1,48) = 0,67$; $P = 0,417$) nor interaction between the factors (compartment x treatment, $F(1,48) = 0,42$; $P = 0,838$), (compartment x groups x treatment, $F(1,48) = 1,538$; $P = 0,221$) or (groups x treatment, $F(1,48) = 0,066$; $P = 0,799$), suggesting that both groups regardless treatment displayed preference for the social stimulus. In the social novelty phase, for time spent with familiar and novel rat, significant differences was noted between compartments ($F=(1,48) = 8.262$; $P=0.006$) and for interaction between compartment x groups ($F= (1,48) = 4.793$; $P= 0.033$), suggesting that control animals exhibited preference by social novelty and that experimental animals displayed deficit in social discrimination unaffected by the treatment with diazepam. In the elevated plus maze (EPM), for time spent in the open arms, significant effects of interaction between factors treatment x groups ($F(1,48) = 9,873$, $P =0,003$) and between groups ($F(1,48) = 4,859$, $P=0,032$) were observed. For total of entries, significant effects of interaction between factors treatment x groups ($F(1,48) = 8,188$ $P=0,0062$) and the treatment ($F(1,48) = 4,412$; $P=0,0062$) were noted. The EPM results suggest that experimental group exhibited anxiety related behavior reverted by the treatment with diazepam. The results suggest that the neonatal SE in male rats produces deficit in social discrimination unrelated to emotionality, being probably caused by social memory impairment. Sponsored by CNPq and PIBIC-Mackenzie

Disclosures: **R.M. Cysneiros:** None. **I.S. Leite:** None. **A.S.S. Castelhano:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.07. Epilepsy

Support: Indian Council of Medical Research, New Delhi, India (45/33/2010/PHA-BMS)

Title: Epilepsy induced depression and memory deficit: Intricacies of Serotonergic System

Authors: ***A. MISHRA**[1,2], R. K. GOEL[2];
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Abstract: Serotonergic interplay (with different receptor subtypes) in the cortex and hippocampus appears to be one of the important common neurochemical interplay leading to epileptogenesis, depression, learning and memory impairment. Role of different receptor subtypes of serotonin has long been implicated in epileptogenesis, depression, learning and memory impairments, but their role in epilepsy induced comorbidities is still unexplored. Therefore this study was envisaged to evaluate the role of different 5- HT receptors (5-HT 1A/2A/2C/3) in kindling induced depression learning and memory deficit. In this study male Swiss Albino mice were kindled using subconvulsive dose of PTZ (35 mg/kg). Once the animals were kindled they were treated with vehicle, 8-OH-DPAT (1 mg/kg/day), WAY-100635 (0.3 mg/kg/day), WAY 100635 + 8-OH-DPAT, DOI (1 mg/kg/day), olanzapine (2 mg/kg/day), olanzapine + DOI, ondansetron (1 mg/kg/day; i.p.), m-CPBG (1 mg/kg/day; i.p.) and ondansetron + m- CPBG for 20 days. Seizure severity score, depression like behavior, learning and memory was evaluated on day 5, 10, 15 and 20. After the behavioral evaluations on day 20, animals were sacrificed to estimate different neurotransmitters in discrete brain parts (by HPLC-FD method), nitrite level and AChE activity (microplate reader method). Ondansetron treatment significantly reduced the seizure severity score and improved the depression like behavior, learning and acquisition performance as compared to vehicle treated kindled animals. The effect of ondansetron was reversed by m-CPBG co-treatment. The neurochemical changes in the cortex and hippocampus also supported the behavioral outcome of the study. This study substantiates the role of $5HT_3$ receptor in epilepsy associated depression like behavior, learning and memory deficit in mice. This study creates a rational to explore the use of more selective 5-HT_3 receptor

ligands for comprehensive management of depressive behavior and memory impairment in patients with epilepsy.

Disclosures: **A. Mishra:** None. **R.K. Goel:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

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Topic: C.07. Epilepsy

Support: Epilepsy Foundation Grant

NIH Grant R15NS088776

Title: The effects of an acute flurothyl seizure on associative learning and memory

Authors: ***A. J. HOLLEY**[1], J. N. LUGO, Jr.[2];
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Abstract: Introduction: Past studies that utilized the flurothyl model of seizure induction have demonstrated impairment of spatial learning and memory in both neonatal and adult rats. However, these studies focused on inducing several seizures and much later examining the effects on learning and memory. The impact of a single acute seizure on learning and memory has not been investigated in mice. **Methods:** In this study, we placed an adult male 129SvEvTac mouse in an inhalation chamber. We then exposed the animal to the inhalant flurothyl (infusion rate of 50 μL/min) until a behavioral seizure (wild running with tonic-clonic seizure) was induced. We ran parallel control subjects in an inhalation chamber for the same time as the seizure mice. Either one hour or six hours later we examined associative learning and memory in delay fear conditioning. In delay fear conditioning the animal was first placed in a fear conditioning chamber. We then presented 20s of 80-dB white noise, which was immediately followed by a 0.7-mA footshock (unconditioned stimulus). We administered two presentations of the sound (conditioned stimulus) and shock pairings. We then examined the acquisition of the associative conditioning by testing the mice 24 hr post-seizure. During this testing period we made changes to the fear conditioning chamber to introduce a novel context. We then placed the mice in the testing chamber and measured their freezing behavior in the new context for 3 min. We also measured freezing during presentation of the white noise CS. **Results:** We found that mice that had experienced a single seizure 1 hr prior to training showed a significant impairment

in associative conditioning to the conditioned stimulus compared to controls 24 hr later $t(1,13) = 2.54$, $p < 0.05$. However, the seizure mice were no different in their freezing behavior in the new context compared to controls $t(1,13) = 1.6$, $p = 0.14$. Mice that had experienced a seizure 6 hr prior to training did not show any significant difference in freezing behavior compared to controls 24 hr later when presented with the conditioned stimulus $t(1,9) = 0.81$, $p = 0.44$ or in the new context $t(1,9) = 0.76$, $p = 0.67$. 0.91. **Conclusions:** These findings suggest that a single acute flurothyl seizure induced 1 hr but not 6 hr prior to associative learning impairs long term fear memory. These findings have implications for understanding the acute effect of seizures on acquiring new knowledge.

Disclosures: **A.J. Holley:** None. **J.N. Lugo:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

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Program#/Poster#: 588.05/F40

Topic: C.07. Epilepsy

Support: CIHR

NSERC

Ontario Brain Institute

Title: Cardiorespiratory dysfunction due to hippocampal seizure propagation into the brainstem

Authors: T. SALAM[1], W. NUWISAIT[1], G. MONTANDON[2], R. GENOV[3], J. PEREZ VELAZQUEZ[4], M. DEL CAMPO[1], *P. L. CARLEN[1];
[1]Toronto Western Hosp, Toronto, ON, Canada; [2]Physiol., [3]Electrical Engin., Univ. of Toronto, Toronto, ON, Canada; [4]Neurosci., Hosp. for Sick Children, Toronto, ON, Canada

Abstract: Background: Cardiorespiratory dysfunction with seizures is the leading cause of death in patients with epilepsy. Clinical evidence suggests that respiratory arrest or prolonged apnea may be the initial cause of the cardiorespiratory dysfunction leading to death. We propose that this is caused by convulsive activity spreading from the cerebrum to cardiorespiratory network in the brainstem. Methods: Eleven rats underwent successful craniotomy for custom-made microelectrode array implantation into the cortex, hippocampus and brainstem. These rats were divided randomly into three groups: (i) control (n=3), (ii) low-dose 4-AP (n=5), and (iii) high-dose 4-AP (n=5). The control group (3 rats) were monitored for 2 - 3 months; the weekly

baseline EEGs were recorded to monitor the impact of implantation damage (especially in brainstem) on the EEG and long-term stability of the recording system. The other groups received an intrahippocampal dose of 4-AP (1 to 5 μL at 40 mM). The 4-AP experiments were repeated in 2 more rats without brainstem implantation. Results: The basal iEEG recordings indicated long-term stability of the recording system. The low-dose group (5 rats) was injected with 1 μl of 4AP (40mM) into the right hippocampus and exhibited local electrographic seizures without spread to the brainstem, which suggested that a higher dose was required. The third group (5 rats) received 5 μl of 4AP (40mM). Three of these rats had several electrographic seizures in the hippocampus and this seizure activity spread into the brainstem within 30 minutes. Sometimes seizures originated in the brainstem prior to being apparent in the cerebrum. Brainstem seizure activity was associated with violent motor seizures followed by dyspnea and respiratory arrest along and with cortical EEG flattening. Two more rats who did not undergo brainstem implantation, had similar seizure-related respiratory difficulties following the same higher dose of (40mM) 4AP. Conclusion: These studies show that seizure activity originating in a cerebral hemisphere can spread into the brainstem and cause death by impairing the cardiorespiratory network. Also cortical EEG flattening could be a marker for subsequent respiratory arrest as noted in both the animal model and in human cases.

Disclosures: **T. Salam:** None. **W. Nuwisait:** None. **G. Montandon:** None. **R. Genov:** None. **J. Perez Velazquez:** None. **M. del Campo:** None. **P.L. Carlen:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 588.06/F41

Topic: C.07. Epilepsy

Support: NIH Grant NS088776

Title: Characterization of neonatal ultrasonic vocalization behavior and neurodevelopmental signaling after kainate-induced seizures in mice

Authors: *C. REYNOLDS[1], G. SMITH[2], T. JEFFERSON[1], J. LUGO[1,2];
[1]Dept. of Psychology & Neurosci., [2]Inst. for Biomed. Sci., Baylor Univ., Waco, TX

Abstract: Seizures during early development are known to cause long-term deficits in social behavior, learning, and memory. However, less is known regarding the acute behavioral impacts due to early-life seizures. Ultrasonic vocalizations (UVs) are one tool to measure early

behavioral changes and have frequently been used to examine early communication deficits in mice. On postnatal day (PD) 10 we administered single intraperitoneal injections of 2.5 mg/kg kainic acid to male and female mice to induce continuous seizures (status epilepticus). On PD11 and PD12 seizure and control mice were separated from their dams for 5 minutes, and the quantity and duration of isolation-induced UVs were recorded. We ran a separate cohort of animals with the same seizure induction method then dissected hippocampi to examine protein changes through western blotting on PD 12. On PD11, we did not observe any significant differences in vocalization behavior. However, on PD12 we found that early-life seizures cause suppression of the quantity and duration of UVs emitted only at the 50 kHz range, $p< 0.05$. Western blotting studies on PD12 also revealed a significantly increased ratio of phospho-S6 protein and decreased phospho-FMRP in the seizure group, $p< 0.05$. These studies enhance existing evidence that neonatal vocalizations indicate selective impairments of early communication behavior in mice. In addition, the western blotting data provides new evidence that the mammalian target of rapamycin (mTOR) intracellular signaling pathway may play a role in this early behavioral alteration after seizures.

Disclosures: **C. Reynolds:** None. **G. Smith:** None. **T. Jefferson:** None. **J. Lugo:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 588.07/F42

Topic: C.07. Epilepsy

Support: NIH Grant NS040554

Title: Effect of age and sex on seizure responses in mice

Authors: *T. N. FERRARO[1], G. G. SMITH[3], R. J. BUONO[2];
[1]Dept Psychiatry, [2]Dept Biomed. Sci., Cooper Med. Sch. of Rowan Univ., Camden, NJ; [3]Res. Service, VAMC, Coatesville, PA

Abstract: The age of onset for Epilepsy in humans is highly variable. Infants and children are recognized as being particularly vulnerable to the development of epilepsy but risk falls for this group after about age 10. Epilepsy risk rises again in mid-life and it continues to increase as people grow older. The influence of sex is less pronounced but overall men appear to be at a slightly greater risk for developing epilepsy compared to women. In order to address age- and sex-dependent mechanisms underlying development of epilepsy, we studied seizure responses in

mice using an electroconvulsive shock paradigm. Male and female mice with a C57BL/6 (B6) genetic background were colony bred, weaned at 3 weeks of age and group-housed by sex. Throughout the study they were maintained under standard environmental conditions (12h/12h light dark cycle) with free access to food and water. Mice of various ages between 3 and 18 months were studied (total N = 286; 182 females and 104 males). Seizure responses were tested using a single electrical stimulus delivered from a constant current electroshock unit (model No. 7801, Ugo Basile, Varese, Italy). Stimulus parameters were 60 mA current at 60 Hz with a 0.4 ms pulse width and a 0.2 second stimulus duration. Seizures were scored as generalized tonic-clonic or as progressing to tonic extension of hind limbs. Data were analyzed using ANOVA. Results showed a sex-specific influence of age on seizure expression. Between the ages of 3 and 6 months, male and female mice exhibited a similar seizure response profile with two-thirds of each group expressing tonic-clonic seizures and one-third expressing more intense tonic hind limb extension seizures. At later developmental time points, a significantly greater number of female mice showed tonic hind limb seizures compared to both younger females and to males of the same age. A significantly smaller number of older male mice also expressed tonic hind limb seizures than younger male mice. These results document age- and sex-specific seizure responses in B6 mice and help to establish a model for subsequent elucidation of underlying mechanisms.

Disclosures: **T.N. Ferraro:** None. **G.G. Smith:** None. **R.J. Buono:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 588.08/F43

Topic: C.07. Epilepsy

Title: Effects of adolescent cannabinoid exposure on adult seizure susceptibility and lethality

Authors: *H. H. LOPEZ[1], M. SPRING[2], K. SCHOOLCRAFT[2];
[1]Psychology, Skidmore Col., Saratoga Spgs, NY; [2]Neurosci., Skidmore Col., Saratoga Springs, NY

Abstract: There is substantial evidence that the endocannabinoid system (ECS) is involved in regulating seizure activity. Pharmacological manipulation of the ECS affects seizure intensity and susceptibility in numerous animal models. The current study explored whether chronic administration of cannabinoids during adolescent development increases subsequent, adult seizure susceptibility. 60 male Wistar Kyoto rats were treated with either the synthetic cannabinoid, CP55,940 (0.4 mg/kg, one treatment per day), or vehicle between 35-45 days old.

Subjects were then allowed to mature to adulthood. At 68-69 days of age, subjects were tested for seizure susceptibility using the pro-convulsant, pentylenetetrazol (PTZ). Subjects received an acute injection of either 35 mg/kg or 50 mg/kg PTZ immediately prior to a 30-min behavioral seizure test. PTZ doses were chosen to produce low-moderate levels of seizure activity in control subjects. There were no significant differences between treated and control subjects in: median seizure severity, % who displayed any seizure activity, % who displayed tonic-clonic seizure, or mean latency to first seizure. However, treated subjects had a higher mortality rate (20%) compared to controls (7%), suggesting that adolescent cannabinoid exposure may increase the lethality of severe seizures experienced in adulthood.

Disclosures: H.H. Lopez: None. **M. Spring:** None. **K. Schoolcraft:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

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Topic: C.07. Epilepsy

Support: NIH Grant R01 NS082635

Dravet Syndrome Foundation

Citizens United for Research in Epilepsy

Title: The effect of elevated temperature on seizures and anxiety in GABRG2+/Q390X knockin epilepsy mouse model

Authors: *T. A. WARNER, J.-Q. KANG;
Neurol., Vanderbilt Univ. Med. Ctr., Nashville, TN

Abstract: Febrile seizures and extended syndromes are frequently associated with gene mutations, especially those mutations in *SCN1A and GABRG2.* It has been demonstrated that elevated temperature alone can induce seizures in the $SCN1A^{+/-}$ mouse model associated with epileptic encephalopathy Dravet syndrome. $Gabrg2^{+/Q390X}$ knockin is a novel mouse model associated with epileptic encephalopathy. The objective of the study was to further explore the effect of elevated temperature on genetic mutations associated with febrile seizures using $Gabrg2^{+/Q390X}$ knockin mice and their wild-type littermates. A heat lamp was used to elevate body temperatures of the mice. A temperature probe and controller were used together to monitor the mouse core body temperature and to regulate heating. Pentylenetetrazol (PTZ)

treatment, a reliable method to induce seizures, was used for comparison to evaluate the effect of heat. Electroencephalography (EEG) was simultaneously evaluated to objectively measure seizure-related events induced by elevated body temperatures or PTZ treatment (50mg/kg). Other measures such as temperature change and levels of anxiety were also observed. Compared to the wild-type mice, *Gabrg2*$^{+/Q390X}$ knockin mice were more susceptible to heat-induced myoclonic jerks as well as generalized tonic clonic seizures, but the seizure frequency and mortality associated with seizures were lower than the PTZ treatment. Additionally, the core temperature of *Gabrg2*$^{+/Q390X}$ knockin mice increased more quickly upon heating. The *Gabrg2*$^{+/Q390X}$ knockin mice also engaged in greater jumping bouts in response to the excessive heat, which may suggest heightened anxiety. These findings suggest elevated temperature alone is a provoking factor for seizures in patients associated with *GABRG2* mutations.

Disclosures: T.A. Warner: None. **J. Kang:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 588.10/G1

Topic: C.07. Epilepsy

Support: Citizen United for Research in Epilepsy (CURE)

Dravet Syndrome Foundation (DSF)

NINDS R01 NS082635

NINDS R01 NS 51590

Title: Impaired gabaergic neurotransmission in amygdala and anxiety phenotype in GABRG2+/Q390X knockin epilepsy mouse model

Authors: *C.-Q. ZHANG[1,2], B. MCMAHON[1], T. WARNER[1], R. MACDONALD[1,3], J.-Q. KANG[1,3];
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Abstract: Epileptic encephalopathies have high comorbidity with other neuropsychiatric disorders such as anxiety and are frequently associated with ion channel gene mutations like

SCN1A and GABRG2. However, the molecular underpinnings of the comorbidities of epileptic encephalopathies have never been addressed. GABRG2(Q390X) is a mutation in the GABAA receptor γ2 subunit that is associated with epileptic encephalopathy in two independent pedigrees. The amygdala plays the central role in the CNS in processing afferent and efferent connections related to emotional functioning and is the site of perception of anxiety. We have recently characterized the Gabrg2+/Q390X knockin mouse, which phenocopies the major features of the epileptic encephalopathy Dravet syndrome. In this study, we used live brain slice recordings, biochemistry, immunohistochemistry and confocal microscopy, elevated zero maze and open field test to characterize the anxiety phenotype and its underlying molecular mechanisms. With live brain slice recordings, the pyramidal-like neurons in basolateral amygdala (BLA) had reduced peak amplitude of GABAergic mIPSCs in the Gabrg2+/Q390X mice. With immunohistochemistry and biochemistry, the wild-type γ2 and α1 subunits were reduced in amygdala. In elevated zero maze test, the heterozygous Gabrg2+/Q390X knockin mice spent increased time in the closed arm, decreased time in the open arm and decreased entries into the open arm. With the open field test, the mice had increased distance traveled and spent less time in the center. Future studies will test the GABAergic neurotransmission in the central amygdala medial sector (CeM) of Gabrg2+/Q390X mice and determine if treatment with diazepam, a positive allosteric modulator of GABAA receptors, can rescue the anxiety phenotype.

Disclosures: C. Zhang: None. **B. McMahon:** None. **T. Warner:** None. **R. Macdonald:** None. **J. Kang:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

Location: Hall A

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Program#/Poster#: 588.11/G2

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant G12 MD007601

NIH Grant R01 DK47320

Title: Competition between the brain and testes for selenium utilization: insights into gender differences in selenium metabolism and risk of neurodevelopmental disease

Authors: *M. W. PITTS[1], P. M. KREMER[1], A. C. HASHIMOTO[1], D. TORRES[1], C. N. BYRNS[1], C. S. WILLIAMS[2], M. J. BERRY[1];

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Abstract: Selenium is essential for both brain development and male fertility. Male mice lacking two key genes involved in Se metabolism (*Scly*$^{-/-}$*Sepp1*$^{-/-}$ mice), selenoprotein P (Sepp1) and Sec lyase (Scly), develop severe neurological dysfunction, neurodegeneration, and audiogenic seizures that manifest beginning in early adulthood. We demonstrate that prepubescent castration of *Scly*$^{-/-}$*Sepp1*$^{-/-}$ mice rescues maturation of GABAergic inhibition, prevents behavioral deficits, attenuates neurodegeneration, and increases brain selenoprotein levels. Moreover, castration also yields similar neuroprotective benefits to *Sepp1*$^{-/-}$ and wild-type mice challenged with Se-deficient diets. These studies provide evidence for a competition between the brain and testes for Se utilization that has concomitant effects on neurodevelopment and neurodegeneration.

Disclosures: M.W. Pitts: None. **P.M. Kremer:** None. **A.C. Hashimoto:** None. **D. Torres:** None. **C.N. Byrns:** None. **C.S. Williams:** None. **M.J. Berry:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 588.12/G3

Topic: C.07. Epilepsy

Title: Increased susceptibility to 6-Hz-induced acute seizures and corneal kindling in a triple-transgenic mouse model of Alzheimer's disease

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Abstract: Rationale: Patients suffering from Alzheimer's disease (AD) have an increased risk of developing seizures and epilepsy, but it is not known how the degree of AD neuropathology influences this interaction. In this study, triple-transgenic (3xTg) mice of different ages, which progressively develop both hallmarks of AD, ß-amyloidosis and tau hyperphosphorylation (Oddo et al. 2003), were investigated for their seizure susceptibility as well as changes in epileptogenesis. Methods: Groups of 4- and 12-months old 3xTg mice (n=16, each) harboring three mutant human transgenes (presenilinM146V, APPSwedish mutation and tauP301L) and age-matched wild type (WT, n=17 and n=14, respectively) mice of both sexes were used. Mice underwent a behavioral test battery (modified Irwin screen, activity cage, elevated plus maze)

and, thereafter, were stimulated via corneal electrodes (6 Hz, 0.2 ms rectangular pulse width, 3 s duration) to determine CC50 via staircase method. Furthermore, mice were kindled by twice daily corneal stimulation (3 mA, 3 s, 50 Hz) for 17 days. Seizure severity was scored according to a modified Racine scale. Results: Irwin screen revealed increased activity and spatial locomotion in 12-months old 3xTg mice compared to corresponding WT mice. Both, 4- and 12-months old 3xTg mice were hyperexcitable (response to touching and elevation at the tail) compared to age-matched WT mice. Increased activity as well as increased horizontal (time spent in and number of visits to the center) and vertical (number of and time spent rearing) explorative behavior was found in 12 months old 3xTg mice compared to corresponding WT mice. Elevated plus maze test did not reveal differences between WT and 3xTg mice. CC50 for 6-Hz-induced seizures was lower in 4-months old (10.5 vs. 17.4 mA, p=0.00002) as well as 12-months old (11.1 vs. 17.8 mA, p=0.00027) 3xTg mice compared to age-matched WT mice. Moreover, the kindling process was age-independently accelerated in 3xTg mice. Conclusion: Mice exhibiting AD neuropathology show hyperactive and hyperexcitable behavior, which is currently discussed as a potential preclinical biomarker for an increased risk to develop epilepsy. Strikingly, increased seizure susceptibility and accelerated epileptogenesis exist already at a pre-plaque age, indicating other underlying mechanisms than only the degree of neuropathological burden.

Disclosures: **M. Bankstahl:** None. **J.P. Bankstahl:** None. **W. Härtig:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 588.13/G4

Topic: C.07. Epilepsy

Title: A novel behavioral approach to examining spatial learning and social interaction in a mouse model of temporal lobe epilepsy

Authors: L. D. ORMISTON[1], S. ANGELIDES[1], A. BARTH[1], *I. MODY[2];
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Abstract: Temporal lobe epilepsy (TLE) is the most common form of acquired epilepsy and is often associated with deficits in learning and memory, in addition to depression and anxiety. Neurological insults, including status epilepticus (SE), often induce epilepsy after a period commonly referred to as the latent period, during which epileptogenesis occurs. Here we

examine behavior associated with the epileptogenic period in a unilateral suprahippocampal kainic acid (KA) injection mouse model of SE-induced TLE. We have previously found that post-SE mice demonstrate anxiety-like behavior in an open field before the onset of spontaneous recurrent seizures (SRS). However, many traditional spatial and non-spatial learning tasks are limiting because they may not sufficiently engage the interest or interaction of the individual mouse. We have now developed a novel behavioral task to examine social interaction and both spatial and non-spatial learning and memory in mice. Using a novel odor-familiarizing housing protocol, we test the animal's interaction with familiar (social interaction), moved (spatial change), and novel (non-spatial change) mice separated within social interaction chambers. We compare post-SE mice to sham controls at multiple time points to characterize behavioral deficits associated with epileptogenesis and those apparent after development of SRS. We found that post-SE animals demonstrate diminished recognition of spatial and non-spatial changes compared to sham controls. Observed behavior differences may potentially be used as biomarkers for development of TLE in post-SE populations, as early test results may signal later development of spontaneous recurrent seizures. This novel test offers unique information about mouse interaction and memory behaviors, providing insights not limited to models of epilepsy.

Disclosures: L.D. Ormiston: None. **S. Angelides:** None. **A. Barth:** None. **I. Mody:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

Location: Hall A

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Program#/Poster#: 588.14/G5

Topic: C.07. Epilepsy

Support: EFA Fellowship 337053

Title: A head-fixation protocol allowing electrophysiological, hemodynamic and behavioral measurements in a polygenic rodent model of absence epilepsy

Authors: *C. P. MCCAFFERTY[1], A. KUNDISHORA[1], J. SAMPOGNARO[1], E. JOHNSON[1], N. SMITH[1], Y. SI[1], P. ANTWI[1], A. MORAWU[1], H. BLUMENFELD[2];
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Abstract: Absence seizures (AS), consisting of behavioral arrest and concurrent EEG spike-and-wave discharges, are the most common seizure type of generalized epilepsy syndromes. They are the defining symptom of childhood and juvenile absence epilepsy, syndromes which are associated with learning difficulties, behavioral disorders and other cognitive impairments. The

neural activity underlying AS has yet to be comprehensively characterized, a development that is imperative given the lack of improvement in first-line therapeutics over the past 50 years. Experimental AS have hitherto been studied primarily in anesthetized or neurolept-sedated animals, introducing a difference in arousal state from the clinical condition that may explain discrepancies observed in hemodynamic responses. Consequently, the establishment of a protocol allowing electrophysiological, hemodynamic and behavioral measurements during unadulterated AS is a priority. At the same time, recent evidence suggesting inter-seizure variation in the degree of behavioral arrest calls for a protocol allowing controlled investigation of arousal and the behavioral correlates of consciousness during experimental AS. We have developed a training program to gradually introduce and habituate Genetic Absence Epilepsy Rats from Strasbourg (GAERS) to head fixation within a stereotaxic frame. The method uses incremental familiarization with restraint, minimizing stress to the GAERS in order to facilitate AS expression within the apparatus. A water restriction regime allows the provision of a reinforcing reward for cooperation in each stage, and also primes the animal for stimulus detection and discrimination training concurrently with the fixation habituation. We found that the protocol achieved linear improvement, over a total training period of 1 month, in measures of task cooperation (percentage of time in correct position, duration of training sessions) and decreases in adverse events (escape attempts, biting) and signs of stress (grooming, defecation, urination) (n = 6 rats). Session length, determined by the willingness of the animal to remain stationary within the apparatus, increased from <1 min to >20 min. These results suggest that sessions of sufficient duration for multi-modal electrophysiological and hemodynamic measurements can be achieved while keeping rats in an unstressed condition, providing an opportunity to investigate the physiological and hemodynamic mechanisms of AS in an awake behaving animal model.

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Poster

588. Animal Models of Epilepsy: Comorbidities

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Topic: C.07. Epilepsy

Support: NIH K08 NS069667 (GFB)

CURE SUDEP Award (GFB)

NIH TL1 TR000151-07 (MAH)

Beth and Nate Tross Epilepsy Research Fund (GFB)

Title: Sleep state and circadian time dependent respiratory consequences of seizures and seizure-induced death

Authors: *G. F. BUCHANAN[1,2], K. I. CLAYCOMB[2], M. A. HAJEK[2];
[1]Neurol., Univ. of Iowa, Iowa City, IA; [2]Neurol., Yale Sch. of Med., New Haven, CT

Abstract: Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in patients with refractory epilepsy. SUDEP tends to occur at night, but whether this is a coincidence, or whether this speaks to a specific sleep state-dependent or circadian-dependent mechanism is unknown. Respiratory and cardiac arrest are the most probable etiologies for SUDEP. Control of both breathing and cardiac function is subject to sleep state-dependent and circadian regulation. Seizures themselves are modulated in a sleep state- and circadian-dependent manner. Here we set out to determine whether there are state- and/or circadian-dependent effects of seizures on cardiac and respiratory function that contribute to seizure-related death. EEG, EMG and EKG electrodes were implanted in adult male mice. Seizures were induced with maximal electroshock (MES; 50 mA, 200 ms, 60 Hz) during wakefulness, non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep during mid-day and mid-night and EEG, EMG, EKG, and breathing were assessed. Vigilance state was determined on-line in real time based on EEG and EMG characteristics using standard parameters. Seizures that occurred during sleep were more likely to be fatal, especially those induced during REM, and those induced during the daytime. In all instances, death ensued due to primary respiratory arrest. Non-fatal seizures induced during NREM were associated with longer duration post-ictal respiratory suppression, reduced ventilation, and increased respiratory rate variability compared to those induced during waking. All mice died when seizures were induced during REM sleep, therefore this analysis could not be conducted. In addition, there was increased baseline variability in the respiratory rhythm in mice that died compared to those that survived. These data indicate that seizures that occur during sleep can have detrimental effects on breathing which may contribute to increased seizure related death.

Disclosures: G.F. Buchanan: None. **K.I. Claycomb:** None. **M.A. Hajek:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.07. Epilepsy

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EU Marie Curie CIG (294233)

CURE SUDEP research award (280560)

Title: Characterization of Cacna1a knock-in mice as a model for sudden unexpected death in epilepsy

Authors: *E. A. TOLNER[1], I. C. M. LOONEN[2], M. B. HOUBEN[3], M. SCHENKE[2], R. D. THIJS[3], R. A. VOSKUYL[2], M. D. FERRARI[3], A. M. VAN DEN MAAGDENBERG[4]; [2]Human Genet., [3]Neurol., [4]Human Genet. and Neurol., [1]Leiden Univ. Med. Ctr., Leiden, Netherlands

Abstract: Sudden Unexpected Death in Epilepsy (SUDEP) is a devastating complication of epilepsy and difficult to study in humans. Risk factors and mechanisms for SUDEP are largely unknown. In recorded SUDEP cases, post-ictal generalized EEG suppression (PGES) is seen prior to death, more often for seizures occurring during sleep when neuronal inhibition is enhanced. In *Cacna1a* knock-in mouse mutants carrying a severe S218L gain-of-function mutation, fatal seizures closely resembling SUDEP were observed. Here we aimed to characterize the relationship of fatal and non-fatal seizures with PGES in the *Cacna1a* mouse model carrying S218L or the milder R192Q knock-in mutation resulting in enhanced excitatory, and presumed intact inhibitory, neurotransmission. Simultaneous EEG and multi-unit activity recordings were performed from somatosensory cortex in awake *Cacna1a* knock-in mice. Video-recording allowed parallel EEG and behavioral analysis of seizures in relation to fatal outcome in homozygous *Cacna1a* S218L mice. In homozygous R192Q and heterozygous S218L mice with a less severe phenotype, epileptic afterdischarges were evoked by electrical stimulation (15s, 8 Hz) of the somatosensory cortex. Up to 3 weeks of brain activity was recorded in freely behaving *Cacna1a* R192Q and S218L mutant mice, as well as in wild-type mice without mutations. Spontaneous seizures were recorded only in the severer S218L *Cacna1a* mutant mice; the majority died from a fatal seizure. All deaths were preceded by suppression of cortical activity, resembling PGES. The occurrence and duration of seizure-related suppression of brain activity were compared between fatal and non-fatal seizures and related to time-of-day and sleep-wake state. Evoked seizures in wild-type, homozygous R192Q and heterozygous S218L mice were

associated with strong EEG suppression and occurrence of cortical spreading depression in mutants. In conclusion, the spontaneous occurrence of fatal seizures typically followed by PGES in homozygous S218L mutants makes *Cacna1a* knock-in mice uniquely suited to investigate SUDEP mechanisms. Comparison of evoked seizure-PGES characteristics among wild-type, R192Q and S218L mice allows to assess gene-dosage effects and provide insight in the role of excitation-inhibition balance for PGES.

Disclosures: E.A. Tolner: None. **I.C.M. Loonen:** None. **M.B. Houben:** None. **M. Schenke:** None. **R.D. Thijs:** None. **R.A. Voskuyl:** None. **M.D. Ferrari:** None. **A.M. van den Maagdenberg:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.07. Epilepsy

Support: Brain Canada Multi-Investigator Research Initiative

Title: Increased anxiety and cognitive impairments in a rat model of absence epilepsy: effects of the T-type calcium channel blocker Z944

Authors: *W. N. MARKS[1,2], M. E. CAVANAGH[2], Q. GREBA[2], L. AN[2], S. M. CAIN[3], T. P. SNUTCH[3], J. G. HOWLAND[2];
[1]Physiol., [2]Univ. of Saskatchewan, Saskatoon, SK, Canada; [3]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Genetic Absence Epilepsy Rats from Strasbourg (GAERS) are a commonly used rodent model of childhood absence epilepsy. In addition to the occurrence of absence seizures in 100% of GAERS, research suggests that the animals also display characteristics of psychiatric disorders including heightened anxiety and increased sensitivity to dopamine agonists. However, a detailed behavioural assessment of the strain has yet to be completed. Therefore, we tested male and female GAERS and Non-Epileptic Control (NEC) rats on a battery of anxiety and cognitive tests relevant to psychiatric disorders. Similar to previous research, we found that GAERS showed increased anxiety-like behavior in the elevated plus maze and increased startle to an acoustic stimulus. In a battery of recognition memory tests, GAERS performed similarly to NEC rats on tactile recognition memory; however, their performance was impaired on a visual recognition test with a one hour, but not five minute, delay. The GAERS strain also showed a

profound disruption of crossmodal memory (tactile-to-visual memory) when compared to the NEC strain. The male, but not female, GAERS were also impaired in visual discrimination and reversal learning assessed using an automated task in touchscreen-equipped operant chambers. In a classical fear conditioning paradigm, GAERS showed normal learning and memory to an auditory conditioned stimulus but impaired extinction and reinstatement. Acute administration of the T-type calcium channel blocker Z944 (3 and 10 mg/kg; i.p.) reversed the crossmodal memory deficit in the GAERS rats while impairing memory in NEC animals (10 mg/kg dose). These results suggest that the GAERS strain is useful for studying the comorbidities related to absence epilepsy as well as the cognitive symptoms of some psychiatric disorders. Experiments with Z944 reveal that altered T-type calcium channel activity may underlie certain cognitive deficits in the GAERS strain.

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Poster

588. Animal Models of Epilepsy: Comorbidities

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Support: NSC 102-2320-B-002-001

MOST 103-2320-B-002-057

AIM for Top University Excellent Research Project, 101R7349, 102C101-42 and 103R4000

Title: Role of RBFOX3/NeuN in epilepsy and cognitive impairment

Authors: *H.-S. HUANG, H.-Y. WANG, P.-F. HSIEH, D.-F. HUANG, P.-S. CHIN; GIBMS, Col. of Medicine, NTU, Taipei, Taiwan

Abstract: Epilepsy is a neurological disorder characterized by epileptic seizures and its prevalence rate is 7 out of 1,000 people. Cognitive impairment is a mental disability characterized by poor global intellectual performance and its prevalence rate varies from 3% to 29% due to differences in diagnostic criteria and sample characteristics. It is still unclear about the exact causal mechanism for epilepsy and cognitive impairment. RBFOX3 (NeuN) is a neuron-specific alternative splicing regulator and its disruption has been identified in patients

with epilepsy and cognitive impairment. RBFOX3 promotes neuronal differentiation through alternative splicing of Numb pre-mRNA during brain development. Despite the importance of RBFOX3 in brain development and its relevance in human brain diseases, its physiological role in brain remains unclear. To address this critical question, we decided to further explore RBFOX3 in the hippocampus of mice. Our studies may provide molecular and cellular mechanisms underlying RBFOX3-related human brain diseases such as epilepsy and cognitive impairment.

Disclosures: H. Huang: None. **H. Wang:** None. **P. Hsieh:** None. **D. Huang:** None. **P. Chin:** None.

Poster

588. Animal Models of Epilepsy: Comorbidities

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Support: FAPESP

CNPq

CAPES

FAEPA

FAPESP-CINAPCE

CAPES-PROEX

Title: A historical and critical overview of the contributions of the wistar audiogenic rat (war) strain to neuroscience. Challenging complexity and transdisciplinarity

Authors: *N. GARCIA-CAIRASCO[1,2], E. H. L. UMEOKA[2];
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Abstract: Twenty-five years ago the Wistar Audiogenic Rat (WAR) strain was introduced to the neuroscience community. The WARs, a genetically-selected reflex model susceptible to audiogenic seizures (AS), mimicks acutely tonic-clonic seizures, and chronically (audiogenic kindling, AK) temporal lobe epilepsy. Here we present an overview of historical highlights of the

WAR strain. Seminal Neuroethological, EEG, cellular and molecular data support the WAR strain as a suitable animal model of epileptology. Epilepsy comorbidities, a hot topic in epilepsy research, bring new potential to the use of WARs in fields such as neuropsychiatry, memory/learning, neuroendocrinology and cardio-respiratory autonomic regulation. Behavioral studies with naïve WARs, showed endogenous anxiety, when compared to Wistars, with reduced exploration in the elevated plus maze and the open field. Also, when compared to age-paired Wistars, WARs are smaller, with hyperplasic adrenal gland and higher levels of corticosterone after exogenous ACTH injection. Furthermore, restrained WARs showed corticosterone-dependent (tested with GR and MR antagonists) higher seizure severity during AK, than unstressed animals. WARs have also potential for studies of compulsive behavior, because, when compared to Wistars microinjected into amygdala with oxytocin, a model of compulsion, naïve WARs displayed significant higher grooming behavior. Those neuroendocrine alterations contribute to the higher blood pressure and altered autonomic regulation of the cardiovascular system found in WARs. At the same time, brainstem 5-HT nuclei, associated to respiratory control, are highly compromised in WARs. Such combination of endocrine/autonomic factors is supportive of increased risk factors for sudden unexplained death in epilepsy. The Morris Water Maze test revealed an impairment of reference memory in young WARs, whereas the Novel Object Recognition test indicated a significant deficit in short-term memory in middle age WARs. The detection of altered β-amyloid protein and phosphorylated-Tau in the brain of WARs, together with the above mentioned memory dysfunctions in WARs, encourage the validation of WARs as a model of Epilepsy-Alzheimer disease comorbidities. Collectively, pioneer and recent findings reinforce the complexity associated to WAR alterations, consequent to their genetically-dependent background and seizure experience. We are currently developing more powerful EEG, molecular and behavioral methods, combined with computational neuroscience/network modeling tools to further increase the WAR strain contributions to contemporary neuroscience.

Disclosures: **N. Garcia-Cairasco:** None. **E.H.L. Umeoka:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

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Program#/Poster#: 589.01/G11

Topic: C.10. Trauma

Support: Queen Elizabeth II Scholarship

Alberta Children's Hospital Research Institute

Title: The effects of early life immune programming on outcomes in a rodent mild traumatic brain injury model

Authors: *S. A. CANDY[1], R. MYCHASIUK[2], H. HEHAR[1], I. MA[1], Q. PITTMAN[1], M. J. ESSER[2];
[1]Univ. of Calgary, Calgary, AB, Canada; [2]Alberta Children's Hosp., Calgary, AB, Canada

Abstract: Mild traumatic brain injuries (mTBI) account for 70-90% of brain injuries and are most common in young children and adolescence. Although most symptoms are acute, approximately 10 -15% of children have impaired recovery and may develop long lasting symptoms. Even in cases where the force and type of the injury are similar it is unclear what renders some individuals more vulnerable than others. This would suggest that there are underlying factors that influence the differential outcomes between individuals. In this respect, peripheral inflammation during critical periods of development has been shown to cause long-term changes in brain excitability, as well as increased susceptibility to later-ischemia induced cell death. As neuroinflammation is thought to play an important role in TBI, early inflammatory exposure and immune programming may be one of the contributing factors to the variation in mTBI outcomes. The goal of this study was to determine whether an early life inflammatory event would modulate the behavioural outcomes subsequent to a mTBI in a rat model. In-house bred male and female Sprague Dawley pups from 8 separate litters, were given an intraperitoneal injection of either LPS (100µg/kg) or saline (SAL) on P10, followed by a mTBI or sham injury on P30. One group of rats was sacrificed at 24 hours after injury (*n=32*) and serum and brain tissue were collected to examine acute effects after the mTBI. Another group of rats (*n=60*) underwent a behavioural test battery including: beam-walking, open field, play behaviour and novel context mismatch. Results from the study were consistent with previous mTBI findings and showed some drug and injury interactions. Rats that experienced LPS and TBI had greater impairments in social interactions. The LPS and mTBI group also showed altered working memory, characterized by a poor preference for the object in the novel environment. Brain tissue and serum samples are currently being analyzed for differences in inflammatory markers. These results highlight that some behaviors' might be more susceptible to modulation by early life inflammation and subsequent brain injury. Future studies will attempt to further understand the role of pre-injury inflammation by altering the dosage of LPS and include fear conditioning testing in the behavioural battery after mTBI.

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Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.10. Trauma

Support: MIRECC

Title: Expression pattern of interleukin (IL)-6, 7 and 10 in the CNS of mice

Authors: *P. SZOT[1,3], A. FRANKLIN[1], D. F. LATTEMANN[2,3], M. RASKIND[1,3], E. PESKIND[1,3];
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Abstract: Inflammation of the CNS has been implicated as an important component in several disorders of the brain including traumatic brain injury (TBI). Neuroinflammation is an initial and complex response with the release of various cytokines, chemokines and growth factors from various cell types. At the Northwest Network Mental Illness Research, Education, and Clinical Center (MIRECC), Seattle, a sample of Iraq/Afghanistan combat Veterans who experienced blast trauma mild traumatic brain injuries (mTBI) (median yrs post last blast TBI=4; median number of blast incidents=13) had elevated CSF IL-7 compared with deployed Veterans and civilian samples with no lifetime history of TBI. CSF IL-6 levels were elevated in deployed Veterans both with or without mTBI. Interleukins have been implicated in the response to TBI, but whether their expression is beneficial or harmful to brain tissue remains unclear. Since the interleukins are involved in the response to TBI, it is important to understand where in the CNS these cytokines and their receptors are expressed and what their contribution may be to the long-term response to TBI. To begin to address these questions, we are determining where IL-6, 7 and 10 are expressed in normal mice. Preliminary measurement of IL-7 mRNA expression with *in situ* hybridization indicates a limited pattern of expression, with stronger levels expressed in the central grey, lateral hypothalamus, and medial thalamic nucleus; this expression pattern differs from that of IL-6 mRNA. Data from CNS mapping studies of IL-6, 7, and 10 (and their receptors) will be presented.

Disclosures: P. Szot: None. **A. Franklin:** None. **D.F. Lattemann:** None. **M. Raskind:** None. **E. Peskind:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 589.03/G13

Topic: C.10. Trauma

Support: Swedish Armed Forces R&D

The Swedish Research Council

Karolinska Institutet Funds

Title: Exposure of rats to a mild blast traumatic brain injury: the galanin system

Authors: *L. KAWA[1], S. BARDE[1], U. ARBORELIUS[1], E. THEODORSSON[2], D. AGOSTON[3], M. RISLING[1], T. HÖKFELT[1];
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Abstract: The incidence of traumatic brain injury (TBI) in the combat setting is increasing due to exposure to blast related mechanisms. The literature reports exposure to the primary blast wave alone can result in a mild blast TBI (mbTBI). The rapid changes in pressure as a consequence of the blast wave impact the head and transmit an initial burst of energy to the brain. This type of injury is very distinct to the TBI literature in the civilian population, which are most commonly due to falls and motor accidents. The underlying mechanisms of mbTBI have yet to be characterized due to the 'invisible' nature of this disease. Structurally the brain appears normal, but 15-30% of patients positive for a mbTBI go on to develop, and suffer persistent cognitive and emotional impairments. Post-traumatic stress disorder (PTSD) is one of the most commonly reported anxiety/mood-disorder in veterans, and is symptomatically highly related to mTBI. PTSD is a psychological consequence of exposure to traumatic events, and can manifest itself with or without injury. The peptide galanin is found co-expressed with the monoaminergic neurons in the brain regions where we have previously reported changes in the monoamine systems, following exposure to a blast wave. Galanin is also implicated to play a role in stress and mood disorders. Thus we sought to ascertain its role in the pathobiology of mbTBI using a rodent model of blast TBI. Anaesthetized rats were placed in a rigid metallic holder, which limited acceleration movements of the head and protected the animals' torso, and thereafter exposed to a single blast wave. Our findings indicate significant upregulation in the galanin transcript levels in the locus coeruleus (LC) and dorsal raphe nucleus (DRN), as evaluated by *in situ* hybridization and confirmed by qPCR. In regards to the receptors, galanin receptor 1 is upregulated in the DRN at 1 and 7 d post-exposure, while in the same region galanin receptor 2 is decreased at the later time point. Increases in the galanin transcript levels were also seen in a number of forebrain regions at the earlier time point. We also analyzed levels of the peptide itself, and found at 3d post-exposure increased galanin in several brain regions

including the amygdala and LC. While, at 7d post-exposure the peptide was decreased in the DRN and amygdala. Taken together, the galanin peptide system appears to play a role in the pathobiology of mbTBI and could present a promising target.

Disclosures: L. Kawa: None. **S. Barde:** None. **U. Arborelius:** None. **E. Theodorsson:** None. **D. Agoston:** None. **M. Risling:** None. **T. Hökfelt:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

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Topic: C.10. Trauma

Support: U.S. Army Grant W81XWH-10-1-0623

Title: Temporal profile of chronic motor and cognitive deficits in a rodent model of penetrating ballistic-like brain injury (PBBI)

Authors: *K. L. CAUDLE, R. C. PEDERSEN, J. A. SUN, S. A. BUSGANG, Y. DENG-BRYANT, A. M. BOUTTÉ, L. LEUNG, F. C. TORTELLA, D. A. SHEAR;
Walter Reed Army Inst. of Res., Silver Spring, MD

Abstract: Traumatic brain injury (TBI) remains one of the largest causes of death and disability in the United States resulting in over 2 million emergency room visits per annum, and as many as 15-50% of patients surviving TBI will experience long-term disabilities. Clarification of pathophysiological mechanisms underlying progressive neurobehavioral deficits as well as other co-morbidities associated with severe TBI is required for targeted therapeutic development. This study sought to characterize the long-term recovery profile of neurobehavioral and neuropathological outcomes in a rodent model of severe penetrating ballistic-like brain injury (PBBI). PBBI was induced by stereotactically inserting a perforated steel probe through the right frontal cortex of an anesthetized rat and rapidly inflating the probe's elastic tubing into an elliptical shaped balloon to 10% of total rat brain volume causing temporary cavitation. Motor performance testing was conducted using the rotarod task at sub-acute (1 and 2 weeks) and chronic (1, 3 and 6 months) post-injury periods (sham n=8, PBBI n=12). Cognitive performance was assessed in separate cohorts of animals using a modified Morris water maze (MWM) task (two trials per day) at 1, 3 and 6 months post-PBBI (sham n=10, PBBI n=12). Rotarod testing revealed significant injury-induced deficits beginning at 7 days post-injury and persisting through 6 months with average latencies to fall reduced by 57±7% (PBBI vs. sham; $p < .05$)

across all assessment time points. Similarly, MWM results revealed significant injury-induced deficits in spatial learning performance across all three assessment post-injury periods, with the average latency to find the hidden platform increased by 115±16% (PBBI vs. sham; $p < .05$). Additionally, PBBI-injured rats spent significantly less time searching in the platform target area and significantly greater time in the perimeter (thigmotaxic swimming behavior) during the MWM missing platform trials. Overall, the results of the current study indicate that the PBBI model produces clinically relevant functional deficits which persist into the chronic phase post-injury. Furthermore, our repeated measures behavioral testing paradigms produce the robust gap in performance abilities between injured and sham animals necessary to evaluate putative neuroprotection therapies.

Disclosures: K.L. Caudle: None. **R.C. Pedersen:** None. **J.A. Sun:** None. **S.A. Busgang:** None. **Y. Deng-Bryant:** None. **A.M. Boutté:** None. **L. Leung:** None. **F.C. Tortella:** None. **D.A. Shear:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.10. Trauma

Support: VA CDA-2 (ES)

NIH F32 NS083109 (LEV)

NIH R01 NS080979 (GLW)

NIH P30 NS061800 (OHSU)

Ellison Medical Foundation (GLW)

Title: Granule cells born during post-traumatic neurogenesis functionally integrate into the hippocampus

Authors: *E. SCHNELL[1], L. E. VILLASANA[2], K. N. KIM[1], G. L. WESTBROOK[3]; [1]Portland VA Med. Ctr., Portland, OR; [2]Anesthesiol. and Perioperative Med., OHSU, Portland, OR; [3]Vollum Inst., Portland, OR

Abstract: Traumatic brain injury (TBI) increases hippocampal neurogenesis, which may contribute to cognitive recovery after injury, but it is unknown whether TBI-induced adult-born neurons functionally integrate into the hippocampal network. We assessed the generation, morphology and synaptic integration of new hippocampal neurons after a controlled cortical impact (CCI) injury model of TBI. TBI-induced newborn neurons were labeled using transgenic expression of fluorescent marker proteins. TBI increased the generation, outward migration, and dendritic complexity of neurons born during post-traumatic neurogenesis. However, these cells had profound alterations in their dendritic structure, with increased dendritic branching proximal to the soma and widely splayed dendritic branches. These changes were apparent during early dendritic outgrowth, and persisted as these cells matured. Whole-cell recordings from neurons generated during post-traumatic neurogenesis demonstrated that they are excitable and functionally integrate into the hippocampal circuit. However, despite their wider dendritic fields, we found no differences in the rate of their electrophysiologic maturation, or their overall degree of synaptic integration when compared to age-matched adult-born cells from sham mice. Our results suggest that cells born after TBI participate in information processing, and receive an apparently normal balance of excitatory and inhibitory inputs. However, TBI-induced changes in their anatomic localization and dendritic projection patterns could result in maladaptive network properties. We are currently investigating the mechanisms driving these changes, with the goal of manipulating levels of post-traumatic neurogenesis to better determine its functional significance.

Disclosures: **E. Schnell:** None. **L.E. Villasana:** None. **K.N. Kim:** None. **G.L. Westbrook:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 589.06/G16

Topic: C.10. Trauma

Support: COGNITO

Title: Experimental Traumatic Brain Injury in rats results in a marked increase of translocator protein 18 kDa (TSPO) binding in the vicinity of the brain contusion

Authors: *C. K. DONAT[1], K. GABER[2], J. MEIXENSBERGER[2], P. BRUST[3], L. H. PINBORG[1], J. D. MIKKELSEN[1];
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Abstract: Traumatic brain injury (TBI) can cause long-term disability by several secondary injury mechanisms. Inflammation in the nervous tissue is a crucial process in the injury response and therefore a potential target for treatment and molecular imaging. TSPO, a protein in the mitochondrial membrane, is robustly upregulated by the inflammatory response in the brain, making it a suitable biomarker. We investigated the response of TSPO over time with the selective and clinically relevant radioligand [^{123}I]CLINDE in a rat model of TBI. Male adult Sprague-Dawley rats were randomly assigned to four groups (survival time: 6, 24, 72 h and 28 d). Animals were anaesthetized and subjected to either sham injury, craniotomy or mild-to-moderate (2 mm depth, 4 m/sec) controlled cortical impact injury (CCI). Drug/surgery-naïve animals were included as additional controls. Representative coronal sections were cut and TSPO binding was assessed with *in vitro* autoradiography in the vicinity of the contusion (M1 motor cortex, bregma +3.5 mm posterior, +4.0 mm lateral). [^{123}I]CLINDE binding was nearly uniform in the brains of naïve and sham-operated animals and displaceable (10 µMol/L PK11195) in all groups. At 24 h, injured animals exhibited a significant increase in binding in the whole ipsilateral hemisphere (49%) as well as in the M1 ipsilateral (201%) and contralateral (38%) cortex. [^{123}I]CLINDE binding was maximally increased at 72 h after CCI in the whole ipsilateral (368%) and contralateral (29%) hemisphere and M1 ipsilateral (1076%) and contralateral (32%) cortex. Surprisingly, craniotomy without TBI produced a significant increase in TSPO at 24 h in the ipsilateral M1 cortex (42%) and at 72h in the ipsilateral hemisphere (232%) and M1 cortex (598%). Binding was not significantly different between the groups at 6 h and 28 d. These data strongly suggest [^{123}I]CLINDE to be a suitable radiotracer for the assessment of brain injury after TBI and the monitoring of anti-inflammatory (pharmaco)therapies.

Disclosures: C.K. Donat: None. **K. Gaber:** None. **J. Meixensberger:** None. **P. Brust:** None. **L.H. Pinborg:** None. **J.D. Mikkelsen:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

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Program#/Poster#: 589.07/G17

Topic: C.10. Trauma

Support: Academy of Finland

Title: Two-dimensional unfolded maps for the study of the location, distribution and extent of the cortical lesion following lateral fluid-percussion injury

Authors: *X. E. NDODE-EKANE, I. KHARATISHVILI, A. SIERRA LOPEZ, R. J. IMMONEN, O. H. J. GRÖHN, A. PITKÄNEN;
A.I.V. Institute, Univ. of Eastern Finland, KUOPIO, Finland

Abstract: Information on the anatomical specificity of the cortical lesion following traumatic brain injury (TBI) is useful for understanding the post-traumatic functional outcome. Thus, there is the need for effective techniques in delineating and quantifying the extent of the cortical lesion. The aim of this study was to use the two-dimensional unfolded map technique to identify the anatomical location, distribution and extent of the cortical lesion following TBI in rats, as a first step in understanding its relationship to the post-traumatic functional deficits. Traumatic brain injury was induced in rats using the lateral fluid-percussion injury (LFPI). To visualise the acute lesion, the rat brains were scanned using the T2 weighted MRI at 3 d post-injury. AT 14 d post-injury, the rats were sacrificed and the brains processed for histological assessment of the lesion. To analyse the extent and distribution of the cortical lesion along the anterioposterior axis, several images of the brain in the coronal plane was collected from the T2 weighted MRI (8-9 slices, 1mm thick) (MRI lesion) and the thionin-stained histological sections (12-15 sections, 30um thick) (histology lesion). The length of the lesion was outline on the surface of the cortex on every image using the ImageJ® software and charted onto an unfolded map of the rat cortex. To reveal the lesion boundaries, the edges of the lesion on every slice/section was then connected with each other. The unfolded MRI and histology lesions revealed that, following LFPI, the lesion spread more laterally than medially and extends caudally involving cortical regions such as the ectohinal, perirhinal and entorhinal cortices. Furthermore, the maps showed that the most implicated cortical regions was the visual,parietal, auditory and somatosensory cortices. An estimate of the lesion size showed that MRI lesion was larger than the histology lesion (21.47 ± 1.53 mm2 vs. 13.15 ± 1.46 mm2, $p<0.001$), probably due to the resolution of the acute post-injury oedema. This data suggested that an unfolded map of the cortical lesion following TBI can be used to obtain precise anatomical information on the distribution and extent of the lesion in the different cortical region.

Disclosures: X.E. Ndode-Ekane: None. **I. Kharatishvili:** None. **A. Sierra Lopez:** None. **R.J. Immonen:** None. **O.H.J. Gröhn:** None. **A. Pitkänen:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 589.08/G18

Topic: C.10. Trauma

Support: CDMRP W81XWH-13-2-0018

Title: Concomitant increase in cognitive behavioral deficits and white matter injury markers over time in a gyrencephalic animal model of traumatic brain injury

Authors: *S. C. SCHWERIN[1], E. HUTCHINSON[2], K. RADOMSKI[1], C. PIERPAOLI[2], S. L. JULIANO[1];
[1]Anatomy, Physiol. and Genet., Uniformed Services Univ., Bethesda, MD; [2]NIH, Bethesda, IL

Abstract: Rodent models of traumatic brain injury (TBI) provide important insight into mechanisms of damage and plasticity following injury, however the low volume of white matter and lissencephalic cortex of the rodent reduce their relevance to study human pathology. The ferret is the smallest mammal with a convoluted brain and the ratio of white to gray matter is comparable to humans. This suggests that the biomechanical response to impact is comparable to human injuries. We investigated injury progression (MRI and immunohistochemistry) and resulting behavioral changes following a mild controlled cortical impact (CCI) in ferrets. We used fifteen adult (5-8 month old) male ferrets; 12 CCI animals were randomly divided into 4 survival time-points (24 hour, 1 week, 4 week, 16 week) and 3 control animals that survived 16 weeks. *In vivo* MRI scans were acquired at baseline and at 1 day post injury (DPI), 7 DPI, 4 weeks post injury (WPI) and 16 WPI. T1 weighted SPGR scans (TE/TR=3.5/16ms) and T2W RARE scans (TE=10, 20, 30 and 40 ms, TR=8s) were acquired with 0.5mm isotropic resolution for visualization of anatomy and detection of volumetric and T2W abnormalities. All brains were also imaged *ex vivo*. Behavioral tests (motor: open field, beam walk, righting reflex, gait analysis; cognitive: T maze and novel object recognition) were conducted at baseline, 6 HPI, 1 DPI, 7 DPI, 4 WPI and 16 WPI. Immunohistochemical staining included markers to demonstrate glial fibrillary acid (GFAP), microglia (Iba1), myelin oligodendrocyte glycoprotein, and microtubule-associated protein . With longer survival times increased GFAP and Iba1 staining persisted strongly at the lesion site and at 1-2 mm from the lesion focus. T2 imaging detected abnormalities in the cortex at all time-points. FA was unremarkable, whereas axial diffusivity may be sensitive to chronic white matter changes. Cortical abnormalities were observed with the Trace map and orientation abnormalities using DEC maps weighted by linear anisotropy co-localized with immunolabeling. Immunohistochemical staining revealed a longitudinal increase in microglia, astrocyte and myelin staining in cortex as well as underlying white matter, which was strongest at 16 WPI. Concomitantly, memory impairment seemed to worsen with time (4 WPI and 16 WPI) on the novel object recognition and the T maze tests. Motor impairment was mild immediately (6 HPI and 1 DPI), but recovered with time. CONCLUSIONS. This gyrencephalic animal model of TBI demonstrated an evolution of injury that correlated with

worsening cognitive function and an increase in injury markers in the white matter, strengthening its translational capabilities.

Disclosures: S.C. Schwerin: None. **E. Hutchinson:** None. **K. Radomski:** None. **C. Pierpaoli:** None. **S.L. Juliano:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

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Topic: C.10. Trauma

Support: DoD Grant (W81XWH-13-01-0243)

Title: Mild traumatic brain injury enhances acquisition and impairs retention of fear learning

Authors: *C. LIN, C. WEISS, J. E. PITT, C. CHAN, J. F. DISTERHOFT;
Dept. of Physiol., Northwestern Univ., Chicago, IL

Abstract: Mild traumatic brain injury (mTBI) affects 1.5 million Americans annually, with half of them experiencing an acute loss of consciousness, memory loss, and confusion following the injury. Injury can result from multiple different traumas, including a sports-related impact or from the blast of an improvised explosive device (IED), as experienced by military personnel. mTBI is a known risk factor for Alzheimer's disease (AD) and is also linked to post-traumatic stress disorder (PTSD) among veterans. Despite the growing awareness to these detrimental effects of mTBI, the neuropathology underlying these specific repercussions is still relatively unknown. In order to elucidate these mechanisms, we adopted a model for closed head mTBI using a high-pressure pneumatic cannon to simulate the high-pressure blast experienced by individuals in the military. mTBI was induced in male B6SJLF1 mice by blasting the top of the head with an overpressure of 20 psi lasting 1-2 ms. Blasted mice exhibited a longer time to wake than sham-blasted mice. Following one day of recovery after the blast, the mice were trained on trace fear conditioning. After conditioning, the mice were tested daily for memory of context and cue retention for five days. Blasted mice acquired fear-conditioning more robustly than sham-blasted mice, as determined by percent freezing. Sham-blasted mice, however, retained the contextual memory of the fear conditioning better than blasted mice. Both groups exhibited equivalent cued fear responses. The enhanced acquisition of the fear conditioning by blasted animals, which has not previously been demonstrated in a mouse model of mTBI, is indicative of more fear-like behavior and correlates with symptoms of PTSD in humans. The poorer retention

of contextual memory is in accordance with previous data showing memory disturbance following mTBI. Studies are currently ongoing to investigate the effect of mTBI on a mouse model of AD (5xFAD mouse model) in fear conditioning to understand the convergence of mTBI and AD pathology on PTSD-like behavior. We hypothesize that mTBI will exacerbate the amyloid pathology and result in more severe learning and memory deficits in blasted mice. The results of this study will aid ongoing research in establishing therapeutics for those suffering from the consequences of mTBI.

Disclosures: C. Lin: None. **C. Weiss:** None. **J.E. Pitt:** None. **C. Chan:** None. **J.F. Disterhoft:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

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Program#/Poster#: 589.10/G20

Topic: C.10. Trauma

Support: Alberta Children's Hospital Research Institute

Markin USRP in Health and Wellness, University of Calgary

Title: An investigation into the role of the nucleus accumbens in mild traumatic brain injury and impulsivity

Authors: *H. HEHAR[1], B. KOLB[3], K. YEATES[2], M. J. ESSER[2], R. MYCHASIUK[2]; [1]Room 274, [2]Univ. of Calgary, Calgary, AB, Canada; [3]Univ. of Lethbridge, Lethbridge, AB, Canada

Abstract: Children characterized as impulsive often engage in risky behaviours that may place them at greater risk for the acquisition of concussions. In addition, parents often report that their children display increased impulsivity and decreased attentional processing following concussion. Studies related to addictions have demonstrated that altered functioning of the nucleus accumbens (NAc) is associated with impulsive behaviour. The purpose of this study was to investigate the effects of a concussion on the NAc, with the primary focus being impulsivity and attentional processing, before and after the injury. This was supplemented with neuroanatomical (Golgi-Cox) and epigenetic (qRT-PCR) analysis. Juvenile Sprague Dawley rats from two distinct cohorts (Impulsive and Standard) were trained in the 5-Choice Serial Reaction (5-CSR) paradigm on the Go/No-Go task for 18 consecutive days. On postnatal day 45 (P45) rats

were tested in the Go/No-Go task and then received a mTBI or sham injury. Animals returned to daily Go/No-Go training from P47-P61, which was followed by extinction testing from P62-P64. Rats in the impulsive cohort were significantly more impulsive than rats in the standard cohort in the Go/No-Go task at both testing points (P45; before the injury, and P61; after the injury). In the standard group, the mTBI increased impulsivity at P61. Sex differences were found in response to the mTBI for the impulsive cohort. Female rats in the impulsivity group exhibited similar increases in impulsivity to that of standard rats following the injury, but there were no changes in impulsivity between males groups. In addition, there were no differences in the number of correct Go-responses completed by any of the groups at the pre-injury test period. However, at the post-injury test, all animals with an mTBI obtained significantly fewer correct Go-responses when compared to their sham cohorts, suggesting a deficit in spatial attention. Furthermore, rats in the impulsive cohorts and mTBI groups were significantly impaired on the extinction task. Golgi-cox analysis of the medium spiny neurons in the NAc showed that all rats with a mTBI had increased dendritic branching and decreased spine density. Sex differences were found for dendritic length whereby the mTBI increased length in females but decreased dendritic length in males. Analysis of expression levels of key genes involved in the reward pathway (DRD2, DRD3, DAT, Comt-f) extracted from the NAc is currently under investigation. Underlying differences in the NAc between the impulsive and standard cohorts, in conjunction with the mTBI induced modifications, may be contributing to their impaired behavioural performance.

Disclosures: H. Hehar: None. **B. Kolb:** None. **K. Yeates:** None. **M.J. Esser:** None. **R. Mychasiuk:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

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Program#/Poster#: 589.11/G21

Topic: C.10. Trauma

Support: Alberta Children's Hospital Foundation

Alberta Children's Hospital Research Institute

Title: Variation in the return-to-exercise time interval following pediatric concussion: effects on behavioural and molecular outcomes

Authors: *R. M. MYCHASIUK[1], H. HEHAR[2], I. MA[2], M. J. ESSER[2];
[1]Neurosci., [2]Fac. of Med., Univ. of Calgary, Calgary, AB, Canada

Abstract: Similar to most brain injury research, the ultimate goal for studies on concussion is effective therapeutics. Literature has shown that exercise has positive effects on neuroplasticity, and brain health, suggesting that it may be an important therapeutic resource for recovery from concussion. Unfortunately, the current return-to-play guidelines were established and implemented with little empirical evidence and significantly limit exercise and activity. These guidelines have recently been called into question and the purpose of this study was to investigate their validity by (1) determining the optimal time-to-return to exercise following the injury, and (2) investigating the efficacy of exercise in amelioration of post-concussion symptomology. At postnatal day 21 (P21) Sprague Dawley rats were randomly assigned to live in sex-matched cages of 4; some of which were equipped with running wheels and some were standard cages. On P30 half of the rats received mTBI using the lateral impact device and the other half received sham injuries. The cages with running wheels were randomly divided into 3 groups; (1) had their running wheels returned immediately after the injury (IMD), (2) had their running wheels returned 3 days post-injury (3-Day), (3) had their running wheels returned 7 days post-injury (7-Day). This generated 6 groups; a) sham + Exercise, b) sham + No Exercise, c) mTBI + IMD, d) mTBI + 3 Day, e) mTBI + 7 Day and f) mTBI + no Exercise. Animals were then run through a behavioural test battery that included beam-walking, open field, elevated plus maze, novel context mismatch, and forced swim. At P46 animals were sacrificed and tissue from the prefrontal cortex (PFC) and hippocampus (HPC) was extracted and RNA was used for qRT-PCR. Expression levels of 8 genes were investigated, (Bdnf, Creb, Dnmt1, Fgf2, Mapt, Pgc1-α, Sirt1, and Tert) in both brain regions. Results from the behavioural battery demonstrated that the optimal recovery time for return-to-exercise was dependent upon the task examined and the sex of the rat. For tasks such as beam-walking and novel context, the earlier the rat returned to exercise, the better their performance was. Conversely, for tasks such as the elevated plus maze and forced swim, the optimal time to return-to-exercise was later, at 3 or 7 days post-injury. Results from the qRT-PCR analysis revealed similar outcomes; effects were sex-, injury-, and exercise-dependent. These findings further demonstrate the complexity of concussion research and emphasize that best-practices going forward may require more personalized treatment strategies based upon an individual's sex, pre-existing characteristics, and symptomology tendencies

Disclosures: **R.M. Mychasiuk:** None. **H. Hehar:** None. **I. Ma:** None. **M.J. Esser:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 589.12/G22

Topic: C.10. Trauma

Support: Student Research & Creativity Institute at Saginaw Valley State University

Title: Does acutely placed embryonic neural stem cell therapy induce restoration of function following cortical contusion impact in adult rats reared in an enriched environment?

Authors: *K. MEERSCHAERT, I. HIATT, M. SEARLES, J. SMITH;
Saginaw Valley State Univ., University Center, MI

Abstract: Traumatic brain injury (TBI) is one of the leading causes of disability and mortality, and each year approximately 1.7 million individuals sustain a TBI. Currently, no effective clinical treatments have been found to combat functional and cognitive deficits that occur from TBI. Recent research has found that enriched environment (EE) aids in functional recovery following TBI. Embryonic neural stem cells (eNSC) express neuronal characteristics and have been shown to survive, migrate after transplantation, and improve recovery after functional loss. Furthermore, recent data from our lab shows that combining EE and eNSC therapy improves functional recovery from TBI and appears to increase the survival rate of eNSCs. The purpose of the current study was to examine the effect that acute transplantation of eNSCs, post-injury, may have on eNSC survival, neuroplasticity, and overall functional recovery following a medial frontal cortex (MFC) contusion in rats reared in EE. Thirty, twenty-five day old male Long-Evans rat pups were reared in EE housing. After ninety days in EE, twenty animals received a MFC contusion injury. Seven days post-injury, ten of the injured animals were transplanted with ~100,000 eNSCs in two locations near the lesion. Behavioral analysis was then conducted using the open field task (OFT), Barnes maze (BM), Morris water maze (MWM), rotor-rod (RR), elevated-plus maze (EPM), and the forced-swim task (FST). Following behavioral testing, the animals were euthanized, perfused, and their brains were extracted. The tissue was embedded in paraffin, sectioned, and underwent hematoxylin and eosin staining. Stereological analysis was performed to quantify the number of surviving cells and total cortical volume. That data suggests that injured animals who received eNSCs performed better during the MWM task, when compared to injured animals that didn't receive eNSCs. For the RR task, the data shows no difference between the treated and non-treated animals, although both were significantly impaired compared to intact controls. The data for the EPM shows that intact animals spent significantly more time in the closed arms and significantly less time in the open arms than both injured groups. Although there was no significant difference between the injured groups, the treated animals spent more time in the closed arms and less time in the open arms than the non-treated group. The current data suggests that timing of placement into EE may affect the performance of eNSC therapy and should be explored further.

Disclosures: **K. Meerschaert:** None. **I. Hiatt:** None. **M. Searles:** None. **J. Smith:** A. Employment/Salary (full or part-time):; Saginaw Valley State University.

Poster

589. Traumatic Brain Injury: Animal Models I

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Program#/Poster#: 589.13/G23

Topic: C.10. Trauma

Support: NIH Grant NS-081370 (AJR)

Office of the Dean, Univ. of Tennessee Health Sci. Ctr. (DHH, AJR)

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Title: Abnormalities in coherence of local field potential oscillations in medial prefrontal cortex are linked to lasting perseverative depression and fear following mild traumatic brain injury in a mouse model

Authors: *D. H. HECK[1], Y. LIU[1], M. G. HONIG[1], S. HELDT[1], N. DEL MAR[1], N. H. GULEY[1], W. BU[1], B. M. MOORE[2], A. J. REINER[1];
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Abstract: Mild traumatic brain injury (mTBI) typically results from a closed-head insult after a primary blast shock wave, blow to the head, or head acceleration - deceleration during a collision. It is a frequent occurrence during military combat, sports, recreational activities, and vehicular accidents, and can result in psychological health problems. The brain regions disrupted by mTBI so as to cause neuropsychiatric deficits have not been determined. We used an air-blast mouse model of mTBI [1] to study the link between functional abnormalities in medial prefrontal cortex (mPFC) and fear perseveration and depression, two of the more disabling neuropsychiatric sequelae of mTBI, for which there is currently no treatment. We focused on the coherence of neuronal oscillations because this measure is likely to reflect integrity of network connectivity and function. We used multi-electrode recordings to measure coherence of local field potential oscillations in the mPFC, somatosensory cortex (SSC) and hippocampus (HC). We found that deficits in coherence within the mPFC network but not in the SSC or HC, strongly correlated with behavioral measures of depression and fear at all tested times, up to one year after the mTBI event. By contrast, mice that had experienced a subconcussive air blast or sham treatment showed normal mPFC coherence and no depression or perseverative fear. We have

previously reported that treating mice with a novel drug SMM-189 (a cannabinoid type-2 receptor inverse agonist) ameliorates fear and depression after mTBI [2]. Our electrophysiological data showed that SMM-189 also restored coherence in the mPFC to normal. Our findings thus suggest that coherence of neuronal oscillations in mPFC is tightly associated with and thus possibly causal to the persistent depression and fear after mTBI. The defect in mPFC coherence may act by perturbing signaling between mPFC and other brain regions linked to fear memory and mood, such as amygdala and nucleus accumbens. Our finding that the rescue of mTBI-related fear and depression by SMM-189 is associated with normalization of neuronal coherence in the mPFC suggests that treatments targeting mPFC coherence may be beneficial for ameliorating neuropsychiatric consequences of mTBI. 1.Heldt, S.A., et al., A novel closed-head model of mild traumatic brain injury caused by primary overpressure blast to the cranium produces sustained emotional deficits in mice. Front Neurol, 2014. 5: p. 2. 2.Reiner, A., et al., Motor, Visual and Emotional Deficits in Mice after Closed-Head Mild Traumatic Brain Injury Are Alleviated by the Novel CB2 Inverse Agonist SMM-189. Int J Mol Sci, 2015. 16(1): p. 758-87.

Disclosures: **D.H. Heck:** None. **Y. Liu:** None. **M.G. Honig:** None. **S. Heldt:** None. **N. Del Mar:** None. **N.H. Guley:** None. **W. Bu:** None. **B.M. Moore:** None. **A.J. Reiner:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 589.14/G24

Topic: C.10. Trauma

Support: CNRM funding

DOD W81XWH-13-2-0019

Title: What can the next generation of diffusion MRI methods offer TBI research?

Authors: *E. B. HUTCHINSON[1], A. AVRAM[2], S. SCHWERIN[3], S. JULIANO[3], C. PIERPAOLI[2];
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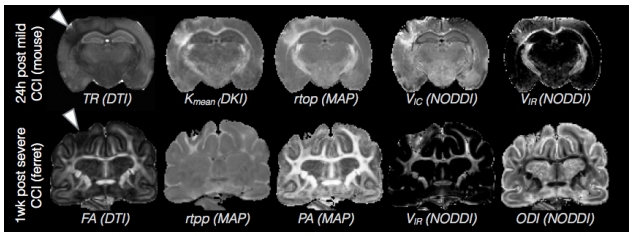
Abstract: Introduction: A new generation of diffusion MRI tools have begun to emerge with promise to provide novel and meaningful imaging markers for traumatic brain injury research

and clinical use. These new MRI tools extend the more standard DWI and DTI methods to measure non-Gaussian features of water movement in tissue as a proxy for the physical manifestations of tissue changes following trauma. The objective of this study was to collate the metrics from several non-Gaussian frameworks calculated using identical diffusion data taken from tissue regions of post-traumatic abnormality. Methods: Brain tissue was evaluated from both mice and ferrets taken during the acute and chronic time periods after induced focal trauma by CCI. Ex-vivo diffusion MRI was acquired for each brain with high spatial resolution and comprehensive sampling of diffusion space. Three imaging frameworks were implemented for these data sets: diffusion kurtosis imaging (DKI), mean apparent propagator (MAP) MRI and neurite orientation dispersion distribution imaging (NODDI). Results: Several important non-Gaussian imaging markers were identified, reproduced and compared with DTI metrics. These results may be seen in the included figure, which reveals heterogeneous metric profiles of abnormalities in spatially distinct subdomains of cortical and white matter tissue.



Metrics abbreviations: TR - trace, FA - fractional anisotropy, Kmean - mean kurtosis, rtop(rtpp) - return to the origin(plane) probability, Vic - intracellular volume fraction, Vir - restricted volume fraction, PA - propagator anisotropy, ODI - orientation dispersion index Conclusions: Each of these new technologies has novel index maps with unique strengths for probing tissue injury that were quantitatively compared with more standard DTI index maps of anisotropy and diffusivity. These new metrics may be used as MRI “stains”, each with strengths and limitations, to better understand the spatio-temporal course of brain changes following trauma.

Disclosures: E.B. Hutchinson: None. **A. Avram:** None. **S. Schwerin:** None. **S. Juliano:** None. **C. Pierpaoli:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 589.15/G25

Topic: C.10. Trauma

Title: Validation of mouse traumatic brain injury model with behavioral and MRI end-points

Authors: *E. LATONUMMI, L. TOLPPANEN, P. PIRINEN, K. K. LEHTIMÄKI, T. AHTONIEMI, A. NURMI;
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Abstract: Traumatic brain injury (TBI) is a leading cause of mortality and survivors of TBI frequently experience long-term disabling changes in cognition and sensory-motor function. Animal models have been developed to replicate the various aspects of human TBI to better understand the underlying pathophysiology and to explore potential treatments. The aim of the current study was to validate cortical contusion injury in mice with behavior assays for functional recovery and T2-MRI imaging. Validation of mouse model will also allow later combination of TBI with transgenic animals and creation of double hit models for TBI research. In order to generate TBI, a computer controlled cortical PinPoint impact was carried out according to Bilgen M. with modifications (Bilgen M, Neurorehabil Neural Repair, 2005). The mice were anesthetized with isoflurane and temperature was maintained at 37.0°C ±1.5°C with a homeothermic blanket system. Cortical contusion was induced in a stereotactic frame. Briefly, a unilateral craniectomy of 3 mm in diameter was performed with the dura kept intact and impact was done with a 2,5-mm-diameter tip traveling at a velocity of 3 m/second and creating a 2 mm-deep deformation. Thereafter the wound was closed with sutures and mice were allowed to recover in homeothermic cages with post-operative care. Functional recovery was monitored with behavioral assays including adhesive tape test, body curl index and rotarod. Lesion volume, edema and tissue viability (T2-relaxation time) were measured with T2-MRI. TBI mice exhibited clear functional deficits and later functional recovery in the behavioral assays for sensory-motor performance. Non-invasive imaging with T2-MRI provided information on the lesion size, edema and tissue viability showing clear lesions as well as increased edema and T2-relaxation time. The validated mouse TBI model offers a tool to study TBI in mice allowing combination with various transgenic lines and making it a valuable model for TBI research and drug discovery.

Disclosures: **E. Latonummi:** None. **L. Tolppanen:** None. **P. Pirinen:** None. **K.K. Lehtimäki:** None. **T. Ahtoniemi:** None. **A. Nurmi:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 589.16/G26

Topic: C.10. Trauma

Support: DGA Grant PDH-1-SMO-1-0202

Title: Long-term cognitive deficits induced by traumatic brain injury in rats are exaggerated by pre-exposure to life-threatening stress

Authors: ***M. O. OGIER**[1,2,3], A. BELMEGUENAI[2,3], S. BOUVARD[2,3], T. LIEUTAUD[2,3], L. BEZIN[2,3];
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Abstract: In the military, traumatic brain injury (TBI) is often sustained under extremely stressful circumstances. However, the influence of such stress on the outcome of TBI has been overlooked. Here, using a rat model, we aimed at determining if behavioral and cognitive outcomes after TBI are affected by prior exposure to life-threatening stress. Adult male Sprague-Dawley rats were stressed by exposure to predator odor 2- 4- 5-trimethyl- 3- thiazoline (TMT) for 7 minutes or were exposed to water (WAT) instead of TMT; exposure was repeated 8 times at irregular intervals over a 2-week period. Two days after the last exposure, rats were subjected to either bilateral mild-to-moderate fluid percussion brain injury (LFP) or Sham surgery. In our 4 experimental groups (Sham-WAT, Sham-TMT, LFP-WAT, LFP-TMT), we measured motor activity and anxiety- like behaviors at 1, 2 and 6 weeks post- trauma, spatial learning and hippocampal long- term potentiation (LTP) at 1 month post- trauma, and basal activity and restraint-stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis at 2 months post-trauma. Compared with Sham-WAT rats, LFP-WAT rats exhibited transient signs of motor hyperactivity but no sign of anxiety at 1 week post- trauma, minor spatial learning and hippocampal LTP deficits, and, finally, lower basal activity of the HPA axis with slightly stronger reactivity to restraint-stress. Exposure to TMT had negligible effects on Sham rats, whereas it exaggerated all deficits observed in LFP rats except for motor hyperactivity. Hence, these data suggest that pre-exposure to stress can aggravate long-term deficits induced by TBI.

Disclosures: M.O. Ogier: None. **A. Belmeguenai:** None. **S. Bouvard:** None. **T. Lieutaud:** None. **L. Bezin:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 589.17/G27

Topic: C.10. Trauma

Support: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - CAPES

Conselho Nacional de Desenvolvimento Científico e Tecnológico - CNPq

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Title: The crustacean central nervous system in focus: nitric oxide induces a specific innate immune response

Authors: *P. CHAVES DA SILVA[1], D. B. PINHEIRO-SOUSA[2], C. CORRÊA[1], S. L. CARVALHO[1], S. ALLODI[1];
[1]Univ. Federal Do Rio De Janeiro, Rio de Janeiro, Brazil; [2]Univ. Federal do Maranhão, São Luis, Brazil

Abstract: The activation of innate immune system after CNS injury is not widely explored in invertebrates. Among few clues available are the results published by our group reporting the recruitment of microglia-like cells expressing inducible nitric oxide synthase (iNOS) 24 h after traumatic injury and secondarily, the recruitment of hyalinocytes - considered immature blood cell - to the lesion site during subacute phase. Glial cells were clearly activated in both stages (Chaves da Silva et al., 2010, 2013). In vertebrates, blood cells and microglia are potentially able to produce nitric oxide (NO) and are important components that integrate the nervous and immune systems during inflammatory processes after injuries to the nervous tissue. Here, we aimed to investigate the cellular/molecular strategy employed 24 and 48 h following ablation of the protocerebral tract (PCT) in animals treated with an inhibitor of iNOS. Adult male crabs Ucides cordatus were injected with L-NIL (dihydrochloride), a specific iNOS inhibitor, 4 h before the unilaterally ablation of eyestalks (in order to cause degeneration of the distal stump of the PCT) to study the contribution of NO to the cell recruitment. L-NIL was also injected 8 h and 20 h after lesion. Using light and electron microscopy, immunohistochemistry and flow cytometry techniques we observed remarkable features in the crustacean CNS. By flow cytometry, we observed a significant decrease of circulating blood cells, especially granular hemocytes, in injured animals treated with L-NIL 24 h after the lesion onset - similar to the control without lesion - when compared with no-treated animals with lesion. By immunohistochemistry, the activation of glial cells and the iNOS expression were also decreased in the lesion site 48 h after L-NIL injections. By immunohistochemistry, light and electron microscopy we also studied and characterized the hematopoietic tissue, which showed cells - hyalinocytes - with similar morphology of those attracted to the lesion site 48 h after lesion, reinforcing the hypothesis that these cells could be immature blood cell migrating to the lesion.

We suggest that iNOS released from granulocytes in the acute phase (24 h) may be responsible to attract other cell types as well as activate glial cells in the subacute phase (48 h). The importance of our study resides in the characterization of cellular and biochemical strategies peculiar of the neurodegeneration in invertebrates. Such events are worth studying in crustaceans because in invertebrates this issue may be addressed with less interference from complex strategies resulting from the acquired immune system.

Disclosures: P. Chaves Da Silva: None. **D.B. Pinheiro-Sousa:** None. **C. Corrêa:** None. **S.L. Carvalho:** None. **S. Allodi:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 589.18/G28

Topic: C.10. Trauma

Support: Starsaward

UTMB start-up funds

Title: *Drosophila* melanogaster as a model for blast-induced traumatic brain injury

Authors: *K. R. BARBER[1], A. M. BUCKLEY[1], B. E. HAWKINS[2], D. S. DEWITT[2], Y. P. WAIRKAR[1];
[1]Neurol., [2]Anesthesiol., The Univ. of Texas Med. Br., Galveston, TX

Abstract: Traumatic brain injury (TBI) is a high priority medical and public health concern, especially veterans. Among veterans deployed to Iraq and Afghanistan, 10-20% suffer deployment related TBI, majority associated with blast exposure (The CDC et al., 2013). Blast-induced traumatic brain injury (bTBI) patients have been diagnosed later with chronic traumatic encephalopathy (CTE), which is characterized by behavior and cognitive impairments including dementia (Goldstein et al., 2015). However, it is unclear why not all TBI patients develop CTE suggesting a genetic component. Postmortem diagnosis of TBI-associated CTE patient´s brain revealed the presence of neurodegenerative disease markers such as hyperphosphorylated tau protein (p-Tau), neurofibrillary and astrocytic tangles, and clustering of neurites around the blood vessels (Mckee et al., 2015). We are using the fruit fly *Drosophila* melanogaster as a model system to unravel the genetic pathway underlying TBI-linked neurodegeneration in CTE. The fruit fly D. melanogaster has been widely accepted as powerful model organism to dissect

the genetic pathway underlying the pathogenic mechanism of various protein aggregations and neurodegenerative diseases. Intriguingly, fruit flies have feature such as an exoskeleton, hemolymph, and glia that represent the human brain and is therefore amenable to TBI. Our preliminary results provide evidence that bTBI reduces lifespan parallel to what is observed in humans after blast injury. To build a successful model we hope to observe p-Tau neurofibrillary tangles and results from D. melanogaster brain sections will be presented. Our preliminary data is promising and suggests bTBI-linked CTE can be modeled in D. melanogaster and it can be very useful to identify the genetic pathway underlying the mechanism of progressive neurodegeneration.

Disclosures: K.R. Barber: None. **A.M. Buckley:** None. **B.E. Hawkins:** None. **D.S. DeWitt:** None. **Y.P. Wairkar:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 589.19/G29

Topic: C.10. Trauma

Title: Electron microscopy of delayed axonopathy following traumatic brain injury

Authors: *C. A. WILEY[1], G. MURDOCH[2], M. SUN[3], J. FRANKS[3], D. B. STOLZ[3], C. E. DIXON[4], G. A. WANG[2], S. J. BISSEL[2], P. M. KOCHANEK[5];
[1]Univ. Pittsburgh, Pittsburgh, PA; [2]Pathology, [3]Cell Biol., [4]Neurolog. Surgery, [5]Critical Care Med., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Traumatic brain injury (TBI) is associated with acute tissue destruction at the site of contusion. However, many patients experience a delayed injury of uncertain etiology. Using a murine model of controlled cortical impact (CCI) and sensitive silver staining, we delineated the nature and extent of injury up to 4 weeks after CCI. Cortical damage at the site of impact varied in severity but followed a stereotypical tissue reaction. More distal neuroanatomically connected sites demonstrated a delayed pathology. This diaschisis consisted of silver positive neuritic processes broadly distributed throughout cortical (e.g. contralateral cortex) and subcortical (e.g. thalamic) sites, beginning as early as 7 days after injury and extending out to 4 weeks. Astrocytic and microglial reaction in these regions was document by immunohistochemistry for GFAP and IBA1 respectively. To further characterize these lesions we developed a novel technique using successive sections to examine the ultrastructure of the silver positive regions. Rather than observing aberrant neurofilamentous structures at the EM level, silver positive neurons and

neurities demonstrated hydropic degeneration. Cellular membranes were preserved despite the loss of mitochondria and cytoskeletal structures including neurofilaments and microtubules. Staining of thalamic regions with Nissl showed "dropout" of identifiable neurons, but electron microscopy showed persistence of the neuronal cell bodies. The morphological preservation of neurons and neuritic processes raises the possibility of reversing the diaschisis and preventing secondary neurodegeneration.

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Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 589.20/G30

Topic: C.10. Trauma

Support: AN 5995

Title: Effects of mild whole-body blast wave trauma to the vestibular receptor organs, nuclei, and VOR in mice

Authors: *S. LIEN[1], S. AJLUNI[2], Z. MRIDHA[1], H. ARNSON[1], N. LEFELDT[1], D. DICKMAN[1,2];
[1]Neurosci., Baylor Col. of Med., Houston, TX; [2]Psychology, Rice Univ., Houston, TX

Abstract: The increased use of close range explosives has led to higher incidence of exposure to blast-related head trauma. Exposure to primary blast waves is a significant cause of morbidity and mortality. Active service members who have experienced blast waves report high rates of vestibular dysfunction, such as vertigo, oscillopsia, imbalance, and dizziness. Accumulating evidence suggests that exposure to blast wave trauma produces damage to both the peripheral and central vestibular system; similar to previous findings that blast-induced damage of auditory receptors. Here we examined the vestibular receptor, central nuclei, and vestibulo-ocular reflex (VOR) behavior in mice after exposure to mild whole body blast wave trauma. Mice were implanted with a head stability post, and the VOR was then measured using a horizontal rotation stimulus (0.5 - 2 Hz; 20 deg/s). Next, each animal was exposed to a single air blast wave overpressure of 55, 75, or 95 kpa while anesthetized and suspended inside a rigid tube. Following blast exposure, animals were allowed to survive for periods of 1, 7, 14, or 28 days. At each survival time point, the VOR was again measured after which the animal was euthanized

and perfused for histological analyses. Vestibular receptors and central nuclei were histologically prepared and the following measures quantified: stereocilia hair bundle counts, density of hair cells (both type I and type II) in the central and peripheral zones, density and size of otoconia in central and peripheral zones, axon density and diameter beneath the stroma. Ongoing measurements also include number and length of axonal initial segment, terminal innervation patterns of calyx, dimorph, and bouton afferents. The medial and lateral central vestibular nuclei were measured for the density of neurons at the caudal, central, and rostral regions of each of these nuclei. The VOR gain and phase of the eye movement responses were compared for the normal (pre-blast) and the blast exposed animals. To date, we have observed a reduction in horizontal VOR gains and stereocilia loss in the highest, 95, kPa blast wave exposed animals. These results suggest that blast-wave exposure can lead to peripheral vestibular damage (possibly central deficits as well) and provides some insight into causes of vestibular dysfunction in blast-trauma victims.

Disclosures: S. Lien: None. **S. Ajluni:** None. **Z. Mridha:** None. **H. Arnson:** None. **N. Lefeldt:** None. **D. Dickman:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 589.21/G31

Topic: C.10. Trauma

Support: NIH Grant NS065866

Title: Efficacy of motor cortical stimulation following experimental TBI is frequency dependent

Authors: *E. R. CLAYTON[1], D. A. KOZLOWSKI[2], T. A. JONES[3], D. L. ADKINS[1]; [1]Neurosci., Med. Univ. of South Carolina, Charleston, SC; [2]Biol. Sci., DePaul Univ., Chicago, IL; [3]Inst. of Neurosci., Univ. of Texas, Austin, Austin, TX

Abstract: In humans and animal models, electrical and magnetic brain stimulation can improve motor function following stroke, especially when paired with rehabilitative training (RT). Previously, we found that following experimental stroke in rats that epidural electrical cortical stimulation (CS) of the ipsilesional sensorimotor cortex (SMC) combined with forelimb RT enhanced motor function and motor cortical plasticity. We also have reported that following experimental traumatic brain injury to the SMC in rats, induced via a controlled cortical impact (CCI), the stimulation parameters previously used in our stroke models improved motor

recovery, but sub-optimally. We have since reported that 100Hz Bipolar epidural stimulation combined with eight weeks of impaired forelimb reach training improves skilled reaching performance compared to Cathodal or Anodal stimulation concurrent with RT. The primary focus of the current study was to determine a more optimal frequency of stimulation. Adult rats that reached criterion on a single-pellet reaching task received a unilateral CCI to the SMC contralateral to the animal's preferred reaching limb. RT was delivered daily for eight weeks alone or concurrently with 25Hz, 50Hz, 100Hz or 350HZ. Animals were also tested in other motor behavioral tasks. We found that 350 Hz Bipolar stimulation combined with RT significantly enhanced motor recovery when compared to RT alone.

Disclosures: E.R. Clayton: None. **D.A. Kozlowski:** None. **T.A. Jones:** None. **D.L. Adkins:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 589.22/G32

Topic: C.10. Trauma

Support: Combat Casualty Care Research Programs #

Title: Differential abundance of amyloid beta peptides in brain tissue and biofluids after delayed recovery from a subacute penetrating ballistic-like brain injury

Authors: *A. M. BOUTTE, B. N. ABBATIELLO, S. F. GRANT, J. S. GILSDORF, D. W. JOHNSON, C. M. CARTAGENA, F. C. TORTELLA, D. A. SHEAR;
Neurosci. and Psychiatry, Walter Reed Army Inst. For Res., Silver Spring, MD

Abstract: Introduction: Severe traumatic brain injury (TBI) is a risk factor for dementias, such as Alzheimer's disease (AD). The degree to which severe TBI produces Aβ pathology remains to be elucidated. Further, the role of Aβ peptides as TBI biomarkers remains debated. This preliminary study sought to determine the effect upon several Aβ peptides and their ratios in a rat model of penetrating ballistic-like brain injury (PBBI). Methods: For PBBI and sham/craniotomy controls, ipsilateral frontal cortex (FC), CSF, plasma, and serum were each collected 1-2 weeks (wks) post-injury (defined as our subacute window of recovery). Aβ38, 40, and 42 quantitation of clarified FC lysate or biofluids was conducted in duplicate using modified ELISAs (Mesoscale, Rockville, MD, USA). Analyte content is displayed as the fold change vs. Sham per time-point. Comparisons between PBBI and Sham groups are discussed ($p \leq 0.05$, 1-tailed t-Test).

Results: In the FC, Aβ40 increased 1.7x after 1wk and Aβ38 increased 1.2x after 2wks. Aβ42 was unchanged. The Aβ42/40 ratio was decreased to 0.56x, but the Aβ40/38 ratio was increased by 1.8x at 1 wk compared to Sham. CSF Aβ38 increased marginally by 1.1x at 1wk, but decreased to 0.85x of sham after 2 wks. Both Aβ40 and 42 increased by 1.3-1.33x 1wk post-PBBI. Interestingly, both of these peptides were reduced to 0.41-0.49x of Sham controls after 2 wks. CSF peptide ratios Aβ 40/38, Aβ 42/38, and Aβ 42/40 were all reduced to 0.48-0.78x compared to Sham levels. Although there was little effect 1wk after PBBI, serum Aβ38, Aβ40, and Aβ42 increased by 2.3x, 1.6x, 3.9x, respectfully, 2 wks after PBBI. In addition, the Aβ42/38 ratio was increased by 3.0x compared to controls at this time-point. Plasma Aβ38 and Aβ40 also increased 2 wks post-PBBI, by 1.2x and 1.1x, each. The plasma Aβ42/38 ratio was 1.3x higher 1 wk after PBBI (but not significant). In contrast, the ratio of Aβ42/40 in plasma was slightly decreased to 0.92x of Sham 2wks after PBBI compared to Sham controls. Overall, Aβ38, 40 and 42 peptides and their inter-peptide ratios were affected in brain tissues and biofluids over time, and the increase within tissues or blood was somewhat proportional to the decreases in CSF during the subacute injury time-frame. Conclusions: The relationship between Aβ38, 40, 42 and their inter-peptide ratios may be key indicators of pre-AD mechanisms in brain tissues affected by TBI. Furthermore, peptide quantitation and their ratios may serve as novel biomarkers of TBI that are (1) detectable during the subacute injury period wherein therapeutic strategies may be stratified and monitored and (2) highly relevant to AD risk. The role of Aβ peptides in TBI warrants further investigation.

Disclosures: **A.M. Boutte:** None. **B.N. Abbatiello:** None. **S.F. Grant:** None. **J.S. Gilsdorf:** None. **D.W. Johnson:** None. **C.M. Cartagena:** None. **F.C. Tortella:** None. **D.A. Shear:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 589.23/G33

Topic: C.10. Trauma

Title: Traumatic brain injury in mice induces chronic hyperesthesia

Authors: J. WU[1], Z. ZHAO[1], X. ZHU[1], N. WARD[1], S. ZHAO[1], *A. I. FADEN[2];
[1]Univ. of Maryland Sch. of Med., Baltimore, MD; [2]Anesthesiol., Univ. of Maryland Med. Ctr., Baltimore, MD

Abstract: Clinical studies indicate that traumatic brain injury (TBI) patients frequently experience chronic post-traumatic pain, particularly vascular-type headache. Although headache

descriptions predominate, patients may also experience allodynia, hyperesthesia, or spontaneous pain. Periorbital and extra-cephalic (paw) mechanical allodynia have been reported in rodent models of TBI, which may persist for weeks after injury. However, there has been little research devoted to understanding the pathobiology to such hyperesthesia. The present study characterized post-TBI sensory changes in mice with mild, moderate or severe controlled cortical impact injury (CCI) by testing mechanical/thermal allodynia, as well as presence of spontaneously face pain. C57BL/6 male mice were subjected to mild, moderate, or severe CCI and mechanical/thermal allodynia as well as mouse grimace scale (MGS) test, a measure of spontaneous pain, were evaluated before and after TBI. The von Frey hair force was significantly decreased on the left hindpaw of mice subjected to moderate or severe TBI when compared to sham operated mice. On the right hindpaw, a significant decreased force was observed in the mice with moderate TBI. The threshold for hot plate temperature was decreased in a severity-dependent manner. The threshold for cold plate was significantly increased in the mice subjected to all grades of TBI severity at early time points (week 1 and 2) but returned to baseline level at 4 weeks post-injury. MGS based on ear position, orbital tightening, and nose bulge was transiently increased at post- TBI day 1 for all groups. Sham and mild TBI group returns to the baseline level at week 1. However, moderate and severe TBI mice showed extended increases of MGS. The present study characterizes the time course of hyperesthesia after TBI of varying severity. These observations indicate that more generalized hyperesthesia and pain, as well as vascular-like headaches, may occur after TBI, and may serve as a model to characterize the pathobiology and potential therapies for such pain.

Disclosures: **J. Wu:** None. **Z. Zhao:** None. **X. Zhu:** None. **N. Ward:** None. **S. Zhao:** None. **A.I. Faden:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

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Program#/Poster#: 589.24/G34

Topic: C.10. Trauma

Support: DoD, W81XWH1110700

Title: Development and validation of an organotypic brain slice model for studying chronic traumatic encephalopathy

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Abstract: Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative condition that occurs as a long-term consequence of repetitive mild traumatic brain injury (TBI). Pathologically, this disease is characterized by abnormal deposition of phosphorylated tau and 43-kDa TAR DNA binding protein (TDP-43), cerebral atrophy and white matter degeneration. Currently, there are multiple *in vitro* and *in vivo* TBI models for studying CTE. However, the lack of consensus on what constitutes an appropriate TBI animal model not only hinders reproducibility but also impedes our understanding the disease mechanisms, which is critical to identifying novel treatment strategies. As an *ex vivo* model that maintains many organ-specific features, organotypic brain slice cultures offer an excellent platform for dissecting the pathophysiology of brain diseases. In the present study, we have established an organotypic brain slice culture model of CTE by subjecting coronal mouse brain slice cultures to repeated mild traumatic brain injury with a Stretch Injury Controller device that delivers pulses of compressed air at a precise rate, resulting in a reproducible blast wave shock injury reminiscent of mild traumatic brain injury. We first compared tissue viability with two different slice culture conditions. Brain slices cultured on the Bioflex membrane possess better cell viability than those on Millicell cell cultures. Next, we cultured brain slices on Bioflex membranes, subjected them to single-blast TBI (4.6 psi) and assessed the neuronal damage. The single TBI induced severe neuronal cell death in cortico-striatal organotypic slices, as determined by propidium iodide uptake assay. We further examined whether repeated mild TBI (mTBI) could induce accumulations of phosphorylated tau and TDP-43 proteins in cortico-striatal organotypic slice cultures. Interestingly, Western blot analysis demonstrated increased phosphorylated tau and TDP-43 in slice homogenates 24 hours after triple-blast exposure. In addition, we confirmed the mTBI-induced gliosis in cortico-striatal organotypic slice cultures by Western blots for the glial markers Iba-1 and GFAP. Together, these results demonstrate that our organotypic brain slice culture recapitulates some key pathological features of CTE in humans and will be amenable for studying the pathophysiological mechanisms as well as for testing potential pharmacological agents for the treatment of CTE (DoD, W81XWH1110700).

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Poster

589. Traumatic Brain Injury: Animal Models I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 589.25/G35

Topic: C.10. Trauma

Support: John D. Dingell VA Medical Center

Department of Psychiatry and Behavioral Neurosciences

Title: Fear conditioning alters excitatory/inihbitory tone in fear learning circuit of mice with mild traumatic brain injury

Authors: *B. SCHNEIDER[1,2], F. GHODDOUSSI[3], J. CHARLTON[1], R. KOHLER[4], M. P. GALLOWAY[5], S. A. PERRINE[4], A. C. CONTI[1,6];
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Abstract: Individuals with mild traumatic brain injury (mTBI) often develop affective changes such as anxiety, depression or symptoms resembling posttraumatic stress disorder (PTSD). It is not clear how mTBI results in PTSD-like symptoms, although studies show changes in activation in brain regions associated with fear learning such as prefrontal cortex (PFC), amygdala (AMY), and hippocampus (HC). Here, we used a mouse model of mTBI to examine the effects of contextual fear conditioning (FC) combined with mTBI compared to the effects of mTBI only. Anesthetized male C57BL/6 mice (10-12 wk) were subjected to either a mild, concussive impact over the sagittal suture of the intact skull, surgery alone, (sham), or handling only (naïve). At 14 d post-injury mice were assessed for fear response (freezing) to FC or left undisturbed. The FC paradigm consisted of 5 distinct phases: habituation, acquisition, extinction, reinstatement, and reinstatement recall. Brains were harvested for proton magnetic resonance spectroscopy (1H-MRS) analysis *ex vivo* at 11.7 T at 25 d post-injury for neurochemical assessment. Naïve and sham groups did not differ on any measures and so were combined to form one group (controls). Mice with mTBI demonstrated increased freezing during acquisition and extinction trials compared to controls. At 25 d post-injury, dorsal HC (dHC) and PFC demonstrated decreased GABA/creatine and GABA/glutamate with mTBI/FC versus mTBI alone, while AMYG showed increased GABA/creatine with mTBI/FC versus mTBI alone. The increased acquisition and slower extinction of conditioned fear observed in mTBI mice resemble facets of FC reported in PTSD patients and observed in those with mTBI. Decreased GABA/creatine in the dHC and PFC, and decreased GABA/glutamate in dHC may reflect reduced inhibitory neurotransmission in these regulatory regions when mTBI is combined with FC, compared to mTBI alone. The increase in GABA/creatine in the AMYG may reflect greater inhibitory neurotransmission when FC is added to mTBI versus mTBI alone. These changes in excitatory/inhibitory tone are also unlike that expected with FC alone, suggesting an interaction between mTBI and FC in the

delayed post-mTBI period that may influence top-down control in the fear learning circuit and affect PTSD-like symptoms.

Disclosures: **B. Schneider:** None. **F. Ghoddoussi:** None. **J. Charlton:** None. **R. Kohler:** None. **M.P. Galloway:** None. **S.A. Perrine:** None. **A.C. Conti:** None.

Poster

589. Traumatic Brain Injury: Animal Models I

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Support: NIH R21NS090244-01

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The State of Indiana

Title: From biomechanics to behavior: an end-to-end investigation of blast-induced traumatic brain injury causes and consequences

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Abstract: The rising incidence of blast-induced traumatic brain injury (bTBI) from terrorist activity, sectarian violence, and military efforts has sparked intense interest in the increasingly prominent public health issue of post-bTBI neurological dysfunction. Linked to neurodegenerative diseases and mental health disorders, bTBI's visibility has grown dramatically over the past decade, garnering substantial coverage in both public news media and the scientific community. A particularly alarming feature of bTBI is its ability to cause brain damage in absence of acutely observable symptoms. So-called mild bTBI have been labeled "silent killers" which preclude early diagnosis and treatment due to their subclinical nature. Numerous instigators and mediators of bTBI damage have been proposed, but mechanistic links between acute biomechanical events during blast exposure and delayed development of behavioral alterations have yet to be established. At present, there have been few reports of the initial consequences of bTBI on brain structure and function and, further, no successful attempts to mechanistically link blast injury mechanics, brain alterations, and ensuing behavioral abnormalities. This precludes well-targeted investigations of novel preventative, diagnostic, and therapeutic measures from being conducted. To this end, we present a rat model and approach

for mechanistically interrogating all stages of bTBI from the injurious insult to eventual behavioral abnormalities. We have obtained real time recordings of brain deformation *in vivo* during bTBI as well as histological and biochemical evidence of mechanical damage to neurons and microvasculature. Further, we have integrated a noninvasive urine biomarker and neurophysiological monitoring via evoked potentials and functional magnetic resonance imaging into our study and demonstrate an ability to distinguish injured from uninjured rats non-invasively. Finally, we have made long-term assessments of behavior and discovered that mild bTBI in our model can recapitulate key end outcomes that transfer to the human post-bTBI clinical presentation including potentiation of Parkinson's disease development and instigation of mental health alterations observed as psychosocial deficits. Further study within this model continuing simultaneous exploration of mechanistic linkages between incident injury, interceding changes in brain morphology, biochemistry, and function observed through neuroimaging and evoked potentials, and eventual behavioral changes will yield new insight capable only when multiple disciplines are utilized together as presented here.

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Poster

589. Traumatic Brain Injury: Animal Models I

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Topic: C.10. Trauma

Support: VA Grant 5IO1RX000375

Title: Studies of repetitive mild TBI: animal model of sports-related head impact

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Abstract: Background: Approximately 1.7 million traumatic brain injuries (TBIs) occur yearly, 80-85% of which are classified as mild. Repetitive mild TBI (rmTBI) has gained worldwide attention for its contribution to higher rates of psychiatric illness, cognitive impairment, and neurodegenerative disease. Chronic traumatic encephalopathy (CTE) is a disease resulting from rmTBI and is believed to contribute to its cognitive and psychiatric manifestations. Three known cellular markers of CTE are GFAP, TDP-43, and p-tau. **Objectives**: Current animal models of TBI are not appropriate for delivering multiple head impacts to the same subject, and the

development of successful therapeutics is contingent upon their translational validity. Current animal models do not fulfill the biomechanical or bio-kinetic requirements to model rmTBI. We have developed a novel method to model sports-related head impact as seen in athletes. To characterize this method, we have assessed selected neuropathological, psychiatric, and cognitive correlates of rmTBI that are known to occur in humans. **Methods**: C57BL/6 male mice are lightly anesthetized with isoflurane and placed under a vertical tube. A weight is pulled upward to a drop height of 1 m and released. Immediately upon impact, the mouse falls onto a foam cushion through a traversable platform. In this arrangement, the impact-induced acceleration and fall always involve a 180° horizontal rotation of the mouse body and free movement of the head upon impact. Mice received a total of 30 head impacts (one per day for 30 consecutive days) with either a 75 g or a 95 g weight. Control animals were anesthetized with isoflurane once per day for 30 consecutive days. Following the final head impact, mice underwent 7 weeks of behavioral testing. Upon completion of behavioral testing, mice were sacrificed and their brains were post-fixed. Immunohistochemistry was used to assess the development of CTE- like neuropathology. **Results**: Mice are delayed in recovering the righting reflex following head impact. Mice show increases in GFAP, Iba-1, p-tau and TDP-43 immunoreactivity following rmTBI. These increases manifest predominantly in the corpus callosum and optic tract. Mice subjected to rmTBI also develop learning and memory impairments and exhibit depression- like behavior. **Conclusions**: We report presently the development of a mouse model that faithfully reflects sports-related head injury in form and outcome. Our method overcomes the limitations of other models while causing the neuropathological and cognitive deficits seen in athletes exposed to multiple head impacts. This neuropathology is seen post-mortem in humans having suffered rmTBI.

Disclosures: **D. Briggs:** None. **M. Angoa-Pérez:** None. **D. Kuhn:** None.

Poster

590. Spinal Cord Injury: Therapeutic Strategies

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RCMI 5G12MD007600

Title: Tamoxifen improves locomotor recovery after spinal cord injury: establishing a therapeutic window for this condition

Authors: *J. M. COLON[1], A. I. TORRADO[1], J. M. SANTIAGO[2], I. K. SALGADO[1], A. CAJIGAS[3], Y. ARROYO[2], J. D. MIRANDA[1];
[1]Physiol. Dept., Univ. of Puerto Rico Sch. of Med., San Juan, PR; [2]Biol. Dept., Univ. of Puerto Rico Carolina, San Juan, PR; [3]Physiol. Dept., Univ. of Puerto Rico Rio Piedras, San Juan, PR

Abstract: Mechanical trauma after spinal cord injury (SCI) initiates a series of cellular and molecular events that lead to necrosis, apoptosis, ischemia, excitotoxicity, gliosis and demyelination. The acute and chronic damage results in loss of sensory-motor function in areas caudal to the lesion epicenter. In the clinical setting, patients arrive at the hospital minutes to hours after the initial insult, which suggests the need to evaluate the effects of a delayed therapeutic intervention. In addition, gender differences exist regarding the outcome after SCI reinforcing the need to establish sex-related differences regarding recovery and response to treatment. We propose the use of Tamoxifen (TAM), a Selective Estrogen Receptor Modulator (SERM) as a therapeutic intervention after SCI. This study aims to determine the beneficial effects of TAM after SCI and the therapeutic window available to administer this treatment. We hypothesized that a continuous TAM administration will improve locomotor function up to 24 hrs after SCI. A laminectomy at the T9-T10 level was performed on adult male and female Sprague Dawley rats (~250 g), which received a moderate contusion to the spinal cord using the NYU impactor. In order to assess a clinically relevant window, TAM pellets (15 mg) were placed subcutaneously at t=0, 6, 12 and 24 hrs for a continuous drug release. Locomotor recovery (BBB Open field test, grid-walk and beam crossing test) was assessed weekly for 35 days post injury (DPI). Male and female TAM-treated rats showed significant functional locomotor improvement after SCI. Delayed TAM administration up to 6 hrs in male rats and 24 hrs in female rats resulted in a significant locomotor improvement after SCI. To establish the mechanism of TAM neuroprotection, a protein expression profile for regenerative, anti-apoptotic and, pro-apoptotic proteins will be determined. Our results suggest that TAM administration activate neuroprotective mechanisms in a clinically relevant setting, which could provide valuable information for the translational properties of this drug into the SCI setting.

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Poster

590. Spinal Cord Injury: Therapeutic Strategies

Location: Hall A

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Topic: C.10. Trauma

Support: Small Project Funding: 201309176211

Small Project Funding: 201409176224

Title: Combined lithium and noggin treatment regulates differentiation of endogenous neural progenitors and promotes functional recovery after spinal cord injury through down-regulation of p300

Authors: *H. K. YIP[1], Y. DAI[2], M. P. L. CHEUNG[2];
[2]Anat., [1]Univ. Hong Kong Fac Med., Hong Kong SAR, China

Abstract: Background: LiCl and noggin inhibits astrogliogenesis through inhibition of GSK-3β/STAT3 and BMP/Smad pathway respectively. We have recently shown that LiCl and noggin promotes neuronal and oligodendroglial differentiation of endogenous neural progenitors (NPCs) and simultaneously inhibited astrocyte differentiation. p300 co-transcription factor bridges between STAT3 and Smad1 leading to an increase in GFAP transcription. Objectives: To examine: (1) the effect of combined LiCl + noggin treatment on the spinal cord (SC)-derived NPC differentiation, astroglial scar formation, axonal regeneration and functional recovery in the chronically injured adult mouse SC, and (2) to investigate the role of p300 in the synergistic effects of the combined treatment. Methods: NPCs were isolated from 4-week-old nestin-GFP transgenic mice and differentiated with LiCl + noggin for 7 days. Four weeks after contusion injury, osmotic minipumps delivering LiCl ± noggin or vehicle were implanted onto the injured SC for 2 weeks. p300 siRNA was injected to the SC tissue in the epicenter. Two weeks later, SC segments were collected for tissue analyses. BDA was injected into the motor cortex to trace the corticospinal tract. BMS test was conducted to examine the locomotor function every week post-SCI. Results: Combined treatment increased the NPC differentiation along neuronal and oligodendroglial lineage while decreased astroglial differentiation. It reduced the size of astroglial scar, decreased GFAP and CSPG expression, promoted axonal regeneration and enhanced BMS scores after chronic SCI. Moreover, combined treatment decreased pSTAT3, pSmad and p300 expression and p300 immunoprecipitated with pSTAT3 and pSmad. p300 siRNA showed a stronger effect than that of the combined treatment on the promotion of oligodendrocyte differentiation and the inhibition of astrocyte differentiation in NPC culture. Knockdown of p300 in injured SC had a similar effect as the combined treatment on NPC differentiation and enhanced remyelination and functional recovery. Conclusions: Combined LiCl and noggin treatment showed a synergistic effect on promoting neuronal and oligodendroglial differentiation of endogenous adult SC- derived NPCs, and concomitantly inhibited astroglial differentiation. These results indicate that combined treatment of LiCl and

noggin after contusive SCI may have significant neurorestorative effects mediated at least partially via p300 down-regulation. Our results suggest the possibility of modulating the expression of p300 as a novel therapeutic strategy to enhance or suppress the formation of astrocytic scar for the treatment of CNS disorders.

Disclosures: H.K. Yip: None. **Y. Dai:** None. **M.P.L. Cheung:** None.

Poster

590. Spinal Cord Injury: Therapeutic Strategies

Location: Hall A

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Program#/Poster#: 590.03/G40

Topic: C.10. Trauma

Title: Use of transplants of mesenchymal stem cells that are genetically altered to overexpress SDF-1 for treating motor deficits in a rat model of spinal cord injury

Authors: *A. N. STEWART[1,2], J. MATYAS[3,2], R. WELCHKO[3,2], A. GOLDSMITH[3,2], E. PETERSON[3,2], S. ZEILER[3,2], M. LU[3,2,4], Z. NAN[3,2,4], J. ROSSIGNOL[3,2,5], G. DUNBAR[3,2,4,6]; [1]Field Neurosciences Inst. At Central Michigan, Mount Pleasant, MI; [2]Program in Neurosci., Mount Pleasant, MI; [3]Field Neurosciences Inst. at Central Michigan Univ., Mount Pleasant, MI; [4]Dept. of Psychology, Mount Pleasant, MI; [5]Col. of Med., Mount Pleasant, MI; [6]Field Neurosciences Inst., Saginaw, MI

Abstract: Strategies using stem cells have demonstrated significant promise for treating and repairing spinal cord injuries (SCI). Most cell therapies aim to either replace lost neural tissue, or preserve tissue from further necrosis during secondary injury cascades, creating a divide between the functional benefits obtained from using neural stem cells and mesenchymal stem cells (MSC) for treating SCI. The goal of the present project was to enhance the migration of neuronal tissue, including endogenous neuronal stem cells, towards the lesion cavity by inducing a gradient of the known chemotaxic protein, stromal derived factor-1 (SDF-1). In addition to examining the migration of neuronal stem cells and axonal projections into or around the transplant site, another aim of this project was to identify the effects of MSC treatment on major histological landmarks, including gliotic scaring, the expression of inhibitory chondroitin sulfate proteoglycans, reduction in inflammation, as well as white matter sparing at seven weeks post injury. Behavioral outcomes were characterized using the Basso Beattie and Bresnahan scale for locomotor recovery, with a novel modified cylinder task to characterize weight-supporting abilities in this severe SCI model. Results suggest that SDF-1 expressing MSC transplants may have potential as a therapeutic option for treating SCI, but further work is needed to increase the potential efficacy

of this approach. Support for this study was provided by the Office of Research and Sponsored Programs at CMU, the College of Medicine, and the Field Neurosciences Institute and John G. Kulhavi Professorship.

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Poster

590. Spinal Cord Injury: Therapeutic Strategies

Location: Hall A

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Topic: C.10. Trauma

Support: Neurotrauma Research Program Grant

Title: Enbrel treatment promotes transplanted donor human mesenchymal precursor cell survival following spinal cord injury

Authors: *S. LOVETT[1], A. R. HARVEY[1], G. W. PLANT[2], S. I. HODGETTS[1];
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Abstract: Immediately following spinal cord injury (SCI), pro-inflammatory cytokines such as tumour necrosis factor alpha (TNFα) and interleukins 1β and 6 (IL-1β, IL-6) are released from damaged cells and other resident cells within the spinal cord. This cytokine release is involved in the inflammatory response to injury and the extensive and persistent spread of secondary damage following SCI. Activation and infiltration of immune cells into the spinal cord contributes to ongoing secondary damage with increased death of neurons and glia, demyelination of intact axons and cyst formation at the injury site. This leads to the development of an adverse environment at the injury site that is inhibitory to axonal regeneration. We have previously shown marked improvements in functional (locomotor) and morphological (tissue sparing, cyst size) outcomes in host tissue following transplantation of adult human mesenchymal precursor cells (hMPCs) into the contused spinal cord in Nude rats. However, donor hMPCs do not survive beyond 4 weeks post transplantation, most likely due to a host immune response. Modulation of pro-inflammatory cytokine levels and immune cell activity immediately following injury may lead to decreased secondary degeneration and increased donor hMPC survival, potentially leading to greater improvement in functional and morphological outcomes. Enbrel is a TNFα antagonist that can have neuroprotective effects following SCI by reducing immune cell

activation, apoptosis and tissue damage. Nude rats were given a moderate contusive SCI and treated with hMPCs alone or in combination with anti-inflammatory Enbrel. Enbrel treatment immediately after SCI improved donor cell survival in all Enbrel+hMPC treated animals, with at least some hMPCs still present in the spinal cord 4 weeks post-transplantation (c.f. two thirds of hMPC only treated animals). These hMPCs were located at the border of the injury and did not appear to migrate from the injection site. Although transplanted hMPC survival was increased, there were no statistically significant improvements in functional recovery at 5 weeks post-injury for any treatment groups. Also, combined Enbrel + hMPC treatment did not further reduce cyst size compared to hMPC transplantation alone. Enbrel may have a moderate impact on SCI repair alone by reducing secondary damage, and may be useful in combinatorial clinical applications to enhance donor stem cell survival in transplantation based therapies.

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Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Topic: C.10. Trauma

Support: CIHR MOP 119278

Title: Inhibiting cortical PKA activity in spinal cord injured rats enhances corticospinal tract plasticity and rehabilitative training efficacy via EPAC

Authors: *K. FOUAD, D. WEI, C. HURD, D. GALLEGUILLOS, J. SINGH, K. K. FENRICH, C. WEBBER, S. SIPIONE;
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Abstract: Elevated levels of the cellular messenger molecule cAMP have frequently been associated with the ability of neurons to sprout and extend neurites, even in the growth inhibitory environment of the central nervous system. A prominent downstream target of cAMP that has been associated with neurite outgrowth is Phosphokinase A (PKA). Here we attempted to demonstrate that also the neuroplasticity promoting effect of rehabilitation training following spinal cord injuries is mediated via PKA activation. However, when we inhibited cortical PKA using Rp-cAMPS during the phase of rehabilitation in spinal cord injured rats to prove this principal, we found the opposite effect. In two independent experiments we discovered that blocking cortical PKA in parallel to rehabilitative training, increased functional recovery and

corticospinal tract sprouting. When we evaluated the effects of the PKA inhibitor *in vitro*, we found that increasing cAMP levels still resulted in increased phosphorylation of a prominent downstream target (i.e., CREB). This however was not found when instead of increasing cAMP a specific PKA agonist was utilized, suggesting that an alternate cAMP dependent pathway was involved. This was proven in an *in vitro* neurite outgrowth essay, where blocking PKA once more increased outgrowth, however when this was combined with an inhibitor for another downstream target of cAMP (EPAC), outgrowth was significantly reduced. It appears that by blocking PKA activity, higher cAMP levels are available for EPAC to increase neurite outgrowth. In conclusion this study shows that although PKA and EPAC act synergistically to translate rehabilitative training induced neuronal plasticity, the increase in EPAC activation is a key to enhanced plasticity. This finding offers new specific pharmacological gateways to boost rehabilitative training.

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Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Support: US Department of Veterans Affairs

NIH

the California Institute for Regenerative Medicine

Title: Optimization of trophic support for neural stem cell grafts in sites of spinal cord injury

Authors: J. ROBINSON[1], L. GRAHAM[1], D. WU[1], Y. WANG[1], M. TUSZYNSKI[1,2], *P. P. LU[1,2];
[1]UCSD, La Jolla, CA; [2]VA-San Diego Healthcare Syst., San Diego, CA

Abstract: Previously we reported that neural stem cells (NSCs) embedded in fibrin matrices containing 9 growth factors and an anti-apoptotic agent, survived and completely filled sites of spinal cord injury. In the current study, we examine whether the number of factors can be reduced while optimizing NSC survival and filling of the lesion site. NSCs derived from embryonic day 14 F344 rat spinal cord (expressing green fluorescent protein, GFP) were

embedded in fibrin matrices containing a defined growth factor cocktail (1 to 4 factors among BDNF, bFGF, VEGF and calpain inhibitor, or original 10 factor combination). Grafts were made into a C5 lateral hemisection of wild-type adult F344 rats two weeks post-injury (N=3-6 per group, total 9 groups). Graft survival was assessed 2 weeks post-grafting. A 4 factor cocktail resulted in graft survival, neuronal differentiation, and filling of lesion site that was equivalent or superior to the 10 factor cocktail. The use of fewer than 4 growth factors, including single growth factors, also frequently but less consistently resulted in NSC survival and fill of lesion site. The effect of fewer growth factors on axon extension from the graft into the host cord is currently under analysis. Collectively, these findings suggest that excellent neural stem cell engraftment and survival can be achieved with a reduced growth factor cocktail, enhancing clinical practicality.

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Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Topic: C.10. Trauma

Support: SCRM Porcine Center Grant

Title: A potent time-dependent suppression of muscle spasticity by spinal-intrathecal delivery of glycine transporter 1 inhibitor (sarcosine) in rat complete thoracic 9 transection model

Authors: *T. YOSHIZUMI, K. KAMIZATO, A. PLATOSHYN, J. STRNADEL, J. A. CORLETO, A. M. ALAMRI, M. R. NAVARRO, J. GIESSINGGER, S. MARSALA, M. MARSALA;
ANETHESIOLOGY, UNIVERSITY OF CALIFORNIA SAN DIEGO MARASALA LAB, LA Jolla, CA

Abstract: Loss of spinal segmental glycinergic inhibition is believed to play a role in the development of spinal injury-induced muscle spasticity. In our previous studies we have characterized the potency of spinal GlyT2 inhibition/silencing in modulating tactile stimulus-evoked spasticity and have demonstrated a paradoxical and time-dependent anti- and pro-spastic effect after a long-term GlyT2 silencing. In our current study, the anti-spastic potency of intrathecal (IT) treatment with glycine transporter 1 inhibitor (sarcosine) in thoracic 9 (T9)

complete transection model of chronic spasticity rat was studied. Adult Sprague-Dawley (SD) rats were used to perform a T8 laminectomy followed a complete T9 transection of the spinal cord. At 2-3 months after transection animals with fully developed muscle spasticity were selected and implanted with a chronic intrathecal catheter placed into lumbar IT space after a partial L5-L6 laminectomy. To measure muscle spasticity EMG response recorded by surface EMG electrodes from gastrocnemius was used and analyzed after applying a progressively increase paw pressure using Von Fray filaments. After baseline spasticity measurement animals received intrathecal bolus injection of: 1) normal saline (10µl), 2) sarcosine 0.25mg, or 3) sarcosine 1mg (in 10µl of saline). After drug or saline delivery the EMG response after paw tactile stimulation was measured at 30, 60, 90, 120 min and at 24 hours. A potent dose-dependent suppression of muscle spasticity was measured after sarcosine administration. Injection of 1mg sarcosine led to a near complete loss of EMG response and this suppressive effect continue for minimum of 120 min after treatment. At 24 hrs the spasticity response returned back to pre-treatment baseline. Saline injection had no detectable anti-spasticity effect. These data demonstrate that pharmacologically-induced spinal GlyT1 inhibition is associated with a potent but transient anti-spasticity effect. Accordingly the spinal GlyT1 system may represent a therapeutical target to ameliorate spinal neuronal hyper-excitability states associated with several spinal neurodegenerative disorders including spinal injury, chronic pain or multiple sclerosis. (Support: SCRM Porcine Center Grant)

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Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Support: DOD W81XWB-10-2-0140

Title: NSAID treatment for whole body vibration-induced pain: effects on behavioral symptoms & spinal activity

Authors: M. ZEEMAN[1], *S. KARTHA[2], B. WINKELSTEIN[1];
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Abstract: Warfighters, pilots, and industrial workers exposed to whole body vibration (WBV) report chronic pain, the severity of which is associated with factors related to the vibration exposure. WBV can cause neck pain, particularly due to loading along the long-axis of the spine. Although there is growing evidence that WBV induces long lasting pain, neurotrophin upregulation in spinal tissues, and inflammation in the spinal cord, effective treatment remains difficult. Even a single vibration exposure at the resonant frequency of the spine produces persistent hyperalgesia, increased PKCε expression in the DRG, and increased CGRP expression and glial activation in the spinal cord. Since ketorolac, a non-steroidal anti-inflammatory drug (NSAID), is an effective analgesic if given after spinal joint pain is established, this study used a rat model to determine if ketorolac, given after WBV exposure, can reduce pain and/or spinal neuronal activity that typically develop. WBV was imposed at 8Hz for 30 minutes under inhalation anesthesia (n=4 rats). Sham rats were exposed only to anesthesia for that same period (n=3). A separate group of rats received ketorolac (10mg/kg i.p.) at 6 hours after the same WBV exposure (n=5). Mechanical hyperalgesia was assessed in the forepaws and hind paws before and 1 day after exposure. On day 1 after behavior testing, electrophysiological recordings were made extracellularly in the C6-C8 spinal dorsal horn under pentobarbital anesthesia (45mg/kg). Evoked neuronal firing was recorded with a carbon fiber electrode for both noxious (10g, 26g) and non-noxious (1.4g, 4g) von Frey stimuli applied to forepaws and analyzed with Spike2. WBV induced hyperalgesia in both the forepaws and hind paws, with significantly lower paw withdrawal thresholds from baseline ($p<0.04$) at day 1; there was no change in threshold after sham or ketorolac treatment with WBV. In fact, on day 1, the ketorolac treatment returned withdrawal thresholds to sham levels, with both paws exhibiting significantly higher withdrawal thresholds than the WBV group ($p\leq0.004$). In general, all stimuli evoked greater numbers of spikes after WBV (31 neurons) than either sham (25 neurons) or NSAID treatment (44 neurons), which were similar to each other. After painful WBV the spike counts were as much as 2.4-fold greater than with NSAID treatment or sham for noxious stimuli and between 1.3 and 1.95 times greater than WBV for non-noxious stimuli. These findings suggest that when given after a painful vibration injury, ketorolac can reduce pain. Additional studies are needed to determine the duration of this effect and the specific effects on spinal neuronal responses and inflammation.

Disclosures: **M. Zeeman:** None. **S. Kartha:** None. **B. Winkelstein:** None.

Poster

590. Spinal Cord Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 590.09/H2

Topic: C.10. Trauma

Support: NIH 5R01NS073636-04 R01

The State of Indiana

Title: Exogenous factors contributing to neuropathic pain after SCI

Authors: *B. MURATORI[1], G. ACOSTA[2], S. M. VEGA ALVAREZ[2], J. PAGE[2], R. SHI[3]; [1]Weldon Sch. of Biomed. Engin., West Lafayette, IN; [2]Dept. of Basic Med. Sci., [3]Weldon Sch. of Biomed. Engin., Purdue Univ., West Lafayette, IN

Abstract: Neuropathic pain (NP) is a debilitating consequence of SCI which is resistant to current analgesic therapies and can greatly degrade the quality of life for SCI victims beyond paralysis. The mechanisms of NP have been widely investigated but are still not well understood. Although most research has been focused on endogenous causality, it is possible that external factors may also contribute to NP which could give insight to the pathogenesis and persistency of NP after SCI. There have been several studies linking cigarette smoking, a known serious threat to human health, to an increase in NP in SCI patients, but no animal study has been attempted to study this further. Acrolein, a neurotoxin present in high quantities in cigarette smoke, has been shown in several animal studies to exist in elevated concentrations in the days to weeks after SCI and also plays a critical role in the degradation of lipids, DNA, and proteins, and consequently, the functionality of neurons in the CNS after injury. In addition, acrolein has been shown to be involved in pathogenesis of NP post SCI. Previous studies with FDA-approved acrolein scavengers have shown that these agents have a neuroprotective effect after SCI in rats by increasing motor function and decreasing NP. In the current study, the inhalation of acrolein at a level equivalent to that emitted from tobacco smoke was shown to exacerbate NP behaviors by up to 60% over the course of two weeks in rats post-SCI. After cessation of acrolein inhalation, pain thresholds returned to the baseline level. The increase in pain coincided with an up-regulation of TRPA1 mRNA expression in the spinal dorsal horn and DRG of animals. TRPA1 is a nociceptor on c fibers of sensory neuron, for which acrolein is a direct agonist. Further, an increase in an acrolein metabolite, 3-HPMA, in urine was shown during the inhalation period, indicating a systemic accumulation of acrolein. This data indicates that cigarette smoke can contribute to neuropathic pain after SCI and that taking measures to reduce smoke-borne acrolein could mitigate post SCI pain. Additionally, and perhaps more importantly, these results further support the mechanistic hypothesis for a key role of acrolein, from both endogenous and exogenous sources, in the genesis of NP after SCI. The ability of acrolein to up-regulate and activate TRPA1 channels indicates that acrolein is a multiple threat in propagating NP, increasing not only activation, but also the sensitivity of TRPA1 to acrolein. Taken together, these data suggest that acrolein may be a novel and effective therapeutic target to alleviate neuropathic pain resulting from both endogenous and exogenous factors after SCI.

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Poster

590. Spinal Cord Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.10. Trauma

Support: Neilsen Foundation 284874

Title: Two-week administration of neuropathic pain medications fails to prevent the development of cutaneously evoked autonomic dysreflexia after high thoracic spinal cord transection in rats

Authors: *K. E. TANSEY, J. CHUNG, H. J. LEE;
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Abstract: In uninjured, pentobarbital anesthetized Long Evans rats, electrical stimulation of thoracic segmental dorsal cutaneous nerves (DCNs) generates a stimulation frequency and nociceptive afferent subtype specific cardiovascular response. To varying degrees, depressor blood pressure (BP) responses and heart rate (HR) increases are seen. We previously found that cervical (C7) spinal cord crush/incomplete injury gives rise to 3 different pathophysiological BP responses to DCN stimulation at 2 weeks, a normal-like depressor response evoked by all DCNs, a dysautonomia response where mixed depressor and pressor effects are evoked from different DCNs, and a pressor response like autonomic dysreflexia (AD) evoked by all DCNs. In all 3 injury groups, the HR increases evoked by DCN stimulation showed prolonged elevation. We also found that the severity of BP pathology is positively correlated with the extent of DCN C fiber sprouting in the dorsal horn and that the prolonged HR responses are correlated with increases in DCN A fiber sprouting there. We have now used a complete T2 spinal cord transection model to produce consistent pressor BP and increased HR responses to stimulation across all DCNs. In this model, we have continuously (twice daily for 2 weeks following injury)

administered 3 neuropathic pain medications commonly used clinically in spinal cord injury (SCI). We used an opioid (Buprenorphine, 0.05 mg/kg), a non-steroidal anti-inflammatory drug (Meloxicam, 1 mg/kg), and an anti-epileptic medication (Gabapentin, 50 mg/kg) to test the hypothesis that continuously treating "pain" could perhaps limit the development of nociception induced autonomic dysfunction after severe high thoracic SCI. Following injury and treatment, segmental DCN stimulation still generated AD cardiovascular responses with pressor BP and increased HR effects in all 3 drug groups. Buprenorphine generated even greater BP increases with caudal (T12, L1) DCN activation. We are currently evaluating whether A and C fiber sprouting in the dorsal horn of these animals tracks with our physiological findings.

Disclosures: **K.E. Tansey:** None. **J. Chung:** None. **H.J. Lee:** None.

Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Topic: C.10. Trauma

Support: NIH R01 NR013601

NIH R21 NR014053

NIH P30 NR014129

Title: Cell cycle activation contributes to development and maintenance of neuropathic pain following spinal cord injury

Authors: ***J. WU**[1], Z. ZHAO[2], C. L. RENN[3], S. G. DORSEY[3], A. I. FADEN[2];
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Abstract: In addition to causing sensorimotor deficits, spinal cord injury (SCI) also results in posttraumatic neuropathic pain in a majority of patients. Chronic pain after SCI may present as hyperalgesia, allodynia, and/or spontaneous pain and is often resistant to conventional pain therapy. Identifying better interventions to manage SCI-PAIN requires improved understanding of the pathophysiological mechanisms involved. After SCI, a key pathophysiological mechanism appears to be cell cycle activation (CCA). We have shown previously that central or systemic early administration of a selective CCA inhibitor reduced CCA, glial changes, and limited SCI-

induced hyperesthesia. Here we compared the effects of early versus late treatment with pan-CDK inhibitor flavopiridol on allodynia as well as presence of spontaneously face pain. Adult C57BL/6 male mice subjected to moderate SCI were treated with daily IP injections of flavopiridol (1 mg/kg), beginning 3 h or 5 weeks after injury and continually for 7 days, mechanical/thermal allodynia as well as mouse grimace scale (MGS) test, a measure of spontaneous pain, were evaluated. We showed that the von Frey hair force, thresholds response to thermal stimulation, and locomotor function were significant improved in early flavopiridol-treated mice when compared to vehicle group. MGS based on ear position, orbital tightening, and nose bulge was transiently increased at day 1 post-injury for all groups. The mice with SCI showed robust and extended increases of MGS up to 3 weeks. Early administration of flavopiridol significantly reduced MGS at week 1 and returned to the baseline level at week 2. Late flavopiridol injection significantly limited hyperesthesia at 7 days after treatment with no effects on locomotion. Thus, our data suggest that cell cycle modulation may provide an effective therapeutic strategy to improve reduce both hyperesthesia and motor dysfunction after SCI. These findings would also markedly expand the potential therapeutic window for such pain.

Disclosures: **J. Wu:** None. **Z. Zhao:** None. **C.L. Renn:** None. **S.G. Dorsey:** None. **A.I. Faden:** None.

Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Topic: C.10. Trauma

Support: LH12024

13-00939S

P304/12/G069

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13-15031P

Title: Anti-inflammatory compound curcumin and mesenchymal stem cells improved recovery from spinal cord injury by altering immune responses in rats

Authors: *J. RUŽICKA[1], L. MACHOVÁ URDZÍKOVÁ[2], A. KLOUDOVÁ[2], C. SHANNON[4], K. KÁROVÁ[2], J. DUBISOVA[2], Š. KUBINOVÁ[2], R. MURALI[4], E. SYKOVÁ[3], M. JHANWAR-UNIYAL[4], P. JENDELOVÁ[2];
[1]Inst. of Exptl. Medicine, ASCR, Praha 4 - Krc, Czech Republic; [2]Neurosci., [3]Inst. of Exptl. Medicine, ASCR, Prague, Czech Republic; [4]Neurosurg., New York Med. Col., Valhalla, NY

Abstract: Spinal cord injury (SCI) is a result of direct injury to the spinal cord, a consequence of which are secondary injuries that cause local subsequent edema and ischemia and hinder the recovery process. The activation of signaling pathways associated with pro-inflammatory cytokines, such as IL-1, IL-6 and IL-15, presents a major obstacle for spinal tract reinervation. Recent studies have suggested that stem cell therapy provides a better option for the treatment and recovery of SCI. Furthermore, the naturally-occurring compound Curcumin longo, an active component present in the spice turmeric, possesses a potent anti-inflammatory property which helps SCI recovery. The objective of this investigation was to use mesenchymal stem cell (MSC) therapy in conjunction with curcumin for an improved and faster recovery from SCI. Methods: Balloon induced spinal cord compression was performed in rats and MSCs (5x 105/50ml) were administered intrathecally seven days after SCI at the site of injury. Curcumin (0.5 mmol/kg or 60 mg/kg) was then given via epidural injection or IP injection with or without MSCs. BBB score, flat beam test and plantar test were used for functional analysis. Secretary inflammatory cytokines (MIP-α, IL-4, IL-1β, IL-2, IL-6, IL-12p70, TNF-α and RANTES) were evaluated at 1, 3, 7, 10, 14 and 28 days post SCI with and without treatments. Results: Recovery from SCI was noticeably greater in curcumin treated rats. All treated animals (curcumin, MSC, curcumin + MSC) showed significant improvement in locomotor behavior in comparison with the saline treated group. The combined treatment of MSCs with curcumin showed a synergic effect in improving locomotor function. Notably, thermal hyperalgesia diminished following treatment with curcumin alone, or in combination with MSCs. Curcumin or MSC treatment preserved white matter and the combination of curcumin and MSCs influenced tissue sparing in the central part of white mater and in the cranial part of gray matter in the injured spinal cords. The levels of cytokines displayed a biphasic effect, where levels of IL-6 and IL-12p70 increased robustly at 28 days, while remaining lower at early stages of injury. In contrast, TNFa showed an increase at day 7, but increased noticeably at day 28 in curcumin and MSC treated groups, along with IL-4, IL-2 and MIP1a. Conclusions: These results provide evidence that curcumin synergistically enhances recovery from SCI when given with stem cells by discretely modulating the immune response at different phases of SCI recovery.

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Poster

590. Spinal Cord Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 590.13/H6

Topic: C.10. Trauma

Support: AUC Grant SSE BIOL AA FY16 No 10

Title: Curcumin decreases secondary damage and improves function following spinal cord injury

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Abstract: Altering the inhibitory micro-environment in the spinal cord that results from the secondary damage following Spinal Cord injury (SCI) has been a major challenge. In the current study we show that Curcumin -a naturally occurring food substance- can provide antioxidant activity that decreases the inflammatory changes and improves functional recovery following a hemi-section SCI model in rats. Our preliminary results show inhibition of the pro-inflammatory cytokine TNF-a and functional improvement on the Grid walk, inclined plane and beam walk functional recovery tests in the treatment group when compared to control groups. Our data support a role for antioxidant food supplements e.g. Curcumin in SCI treatment in combination with other treatment strategies.

Disclosures: S. Abu Hussein: None. **H. Attia:** None. **A.A. Abdellatif:** None.

Poster

590. Spinal Cord Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 590.14/H7

Topic: C.10. Trauma

Support: Craig H. Neilsen Foundation Grant grant 284621

Title: The effect of bone marrow stromal cells on blood spinal cord barrier stabilization after spinal cord injury

Authors: *G. J. RITFELD[1], G. VOLPEDA[2], M. OUDEGA[1];
[1]The Miami Project to Cure Paralysis, Univ. of Miami Miller Sch. of Med., Miami, FL; [2]Univ. of Pittsburgh, PITTSBURGH, PA

Abstract: Bone marrow stromal cell (BMSC) transplantation is a promising strategy for repair of the injured spinal cord. BMSCs have been shown to elicit neuroprotection associated with functional recovery. The exact mechanism behind this BSMC-mediated neuroprotective effect is unknown, but paracrine effects of the numerous growth factors secreted by BMSCs are believed to, at least in part, mediate tissue protection. Among the factors secreted by BMSCs are angioprotective molecules, including vascular endothelial growth factor (VEGF) and angiopoietin-1 (ANG1). Previously, we have shown that BMSCs transplants elicit an angiogenic response. These newly formed blood vessels may mediate the observed neuroprotective effects, but may also contribute to inflammation due to an immature blood-spinal cord barrier and associated blood vessel leakage. In the present study, we studied the effects of BMSC transplants on blood vessel stabilization after spinal injury. We used female adult Sprague-Dawley rats to elicit a moderately severe spinal cord contusion at the ninth thoracic level. Three days later 5 x 10e5 BMSCs were injected in the contusion epicenter and spinal cords were collected at 4 days, 8 days, 17 days, and 4 weeks post contusion. The blood-spinal cord barrier was analyzed structurally with antibodies against occludin and SMI-1 and functionally by quantifying blood vessel leakage after systemic perfusion with Evan's Blue. Our data provides detailed information about BMSCs' effect on blood vessel stabilization after spinal cord injury. Future studies will focus on genetically enhancing Angiopoeitin-1 expression by BMSCs to accelerate blood-spinal cord barrier maturation to enhance tissue repair. This work was funded by the Craig H. Neilsen foundation.

Disclosures: G.J. Ritfeld: None. **G. Volpeda:** None. **M. Oudega:** None.

Poster

590. Spinal Cord Injury: Therapeutic Strategies

Location: Hall A

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Topic: C.10. Trauma

Support: Prize Melo e Castro for Spinal Cord Injury Research - Premios Santa Casa Neurociencias

Title: Combination of adipose stem cells and olfactory ensheathing cells as a treatment for spinal cord injury

Authors: E. GOMES[1], S. MENDES[1], R. SILVA[1], F. TEIXEIRA[1], J. GIMBLE[3], N. SOUSA[1], N. SILVA[1], *A. J. SALGADO[2];
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Abstract: Spinal Cord Injury (SCI) is a highly incapacitating condition for which there is still no treatment. Cellular therapies are seen as a promising tool for SCI repair. From the myriad of cells currently being tested, Adipose Tissue Stem Cells (ASCs) secrete factors that promote neuronal proliferation; in addition, Olfactory Ensheathing Cells (OECs) are characterized by promoting neuronal regeneration and guidance. Interestingly, our group has previously shown that OECs present positive paracrine interactions with ASCs [1]. In this sense, we intend to combine ASCs and OECs, testing their effects on: 1) an *in vitro* model of axonal regeneration, using dorsal root ganglia explants (DRGs); and 2) an *in vivo* hemisection rat model of SCI. DRGs were co-cultured with ASCs/OECs during 4 days, after which axonal outgrowth was measured. *In vivo*, 80.000 cells of a mixture of ASCs and OECs was injected rostral and caudally to the injury site. Animals without treatment were used as controls. The behavioral evaluation included the BBB test, activity box test and average velocity on water. *In vitro* results revealed that OECs alone or in co-culture with ASCs promote the highest increase of neurite outgrowth. Moreover, rats treated with ASCs/OECs presented improved locomotor scores on the BBB scale. Histological analysis revealed a lower inflammatory profile of animals treated with the transplantation of cells. No major alterations were observed in astrogliosis and axonal organization. Overall, these results support the use of these cells as a therapeutic approach for SCI. References [1] Silva NA, Gimble JM, Sousa N, Reis RL, Salgado AJ. Combining adult stem cells and olfactory ensheathing cells: the secretome effect. Stem cells and development. 2013;22:1232-40.

Disclosures: **E. Gomes:** None. **S. Mendes:** None. **R. Silva:** None. **F. Teixeira:** None. **J. Gimble:** None. **N. Sousa:** None. **N. Silva:** None. **A.J. Salgado:** None.

Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Topic: C.10. Trauma

Support: Canadian Institutes of Health Research (CIHR)

Rick Hansen Foundation

Title: Sox9 knockdown promotes reactive sprouting and locomotor recovery in spinal cord injured mice by reducing CSPG levels

Authors: *T. HRYCIW[1], W. M. MCKILLOP[1], N. M. GEREMIA[1], E. M. YORK[2], L. RUBINGER[1], T. LIU[1], K. XU[1], A. BROWN[3];
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Abstract: Chondroitin sulfate proteoglycans (CSPGs) are upregulated by reactive astrocytes both at the glial scar and distal to the lesion following spinal cord injury (SCI). This response may limit plasticity during recovery from injury. We have previously identified the transcription factor SOX9 as a key regulator of CSPG production, and demonstrated that conditionalSox9 ablation leads to decreased CSPG levels and improved recovery of hind limb function after SCI. We now demonstrate increased neural input onto spinal neurons caudal to the lesion in SCI Sox9 conditional knockout mice as indicated by increased levels of the presynaptic markers synaptophysin and VGLUT1. Whereas retrograde tract-tracing studies failed to provide evidence for increased axonal sparing or long-range regeneration in the Sox9 conditional knockout mice, anterograde tract-tracing experiments demonstrated increased reactive sprouting from the corticospinal tract caudal to the lesion after SCI. Finally, inhibiting CSPG degradation in Sox9 conditional knockout mice by administration of an MMP inhibitor prevented the improvements in locomotor recovery observed in untreated Sox9 conditional knockout mice, suggesting that improved locomotor function in these mice after SCI is due to increased reactive sprouting secondary to reduced CSPG levels distal to the lesion. Using computational chemistry we have recently identified Z02 as a putative small molecule inhibitor of SOX9. Z02 reduces SOX9 target gene expression in primary astrocyte cultures. The effects of Z02 on gene expression and locomotor recovery after spinal cord injury in the rat will be presented.

Disclosures: **T. Hryciw:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Named as inventor on patents and patent applications related to SOX9 inhibition.. **W.M. McKillop:** None. **N.M. Geremia:** None. **E.M. York:** None. **L. Rubinger:** None. **T. Liu:** None. **K. Xu:** None. **A. Brown:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Named as inventor on patents and patent applications related to SOX9 inhibition..

Poster

590. Spinal Cord Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.10. Trauma

Support: ERC Starting Grant

Title: A pericyte origin of stromal scar tissue following multiple different types of lesions to the central nervous system

Authors: *Y. KELAHMETOGLU[1], D. DIAS[1], J. TATARISHVILI[3], C. PEREZ ESTRADA[2], A. ERNST[1], L. BRUNDIN[2], Z. KOKAIA[3], O. LINDVALL[3], J. FRISÉN[1], C. GÖRITZ[1];
[1]Dept. of Cell and Mol. Biol., [2]Dept. of Clin. Neurosci., Karolinska Inst., Stockholm, Sweden;
[3]Stem Cell Center, Fac. of Med., Lund Univ., Lund, Sweden

Abstract: Central nervous system (CNS) lesions often lead to long lasting functional deficits due to poor regeneration. One major obstacle is the formation of scar tissue that represents a permanent barrier to regenerating axons. We recently showed that in the injured mouse spinal cord, a discrete subpopulation of perivascular cells lining the microvasculature, termed type A pericytes, are the primary source of stromal cells that form the core of the chronic CNS scar. This study aims to analyze whether type A pericytes are a general source of stromal tissue in various pathologies and throughout the CNS. Using inducible *in vivo* lineage tracing of type A pericytes in combination with different lesion models of the CNS, we compared the contribution of type A pericytes to scar formation. Our results show that type A pericytes contribute similarly to stromal scar tissue formation after a corticostriatal stab lesion in the brain as is seen after spinal cord injury (SCI). We furthermore compared the type A pericyte recruitment in response to transient middle cerebral artery occlusion (MCAO), a model of cerebral ischemia, experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS) and the GL261 glioblastoma model that mimics the human Gliablastoma Multiforme. In all lesion models we observed vascular modulation that led to a change in vessel density and pericyte coverage. Type A pericytes detach from the blood vessel wall and contribute to stroma formation in all models but MCAO, while the extent of recruitment was lesion specific. Our findings reveal pericyte-derived stroma formation in different parts of the CNS and in response to several different lesions and propose type A pericytes as a novel target to interfere with stroma formation.

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Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Topic: C.10. Trauma

Support: NIH Grant NS069765

Title: Effects of reduction of suppressors of cytokine signaling-3 (socs3) expression on dendritic outgrowth and demyelination after spinal cord injury

Authors: K. PARK, C.-Y. LIN, K. LI, *Y.-S. LEE;
Neurosci, Cleveland Clin., Cleveland, OH

Abstract: Suppressors of cytokine signaling-3 (SOCS3) is associated with limitations of nerve growth capacity after injury to the central nervous system. Although genetic manipulations of SOCS3 can enhance axonal regeneration after optic injury, the role of SOCS3 in dendritic outgrowth after spinal cord injury (SCI) is still unclear. The present study investigated the endogenous expression of SOCS3 and its role in regulating neurite outgrowth *in vitro*. IL-6 induces SOCS3 expression at the mRNA and protein levels in neuroscreen-1 (NS-1) cells. In parallel to SOCS3 expression, interleukin-6 (IL-6) induced tyrosine phosphorylation of signal transducer and activator of transcription 3 (STAT3) in NS-1 cells. Lentiviral delivery of short hairpin RNA (shSOCS3) (Lenti-shSOCS3) to decrease SOCS3 expression into NS-1 cells enhanced IL-6-induced tyrosine phosphorylation of STAT3 (P-STAT3 Tyr705) and promoted neurite outgrowth. In addition, we determined if reduction of SOCS3 expression by microinjection of Lenti-shSOCS3 into spinal cord enhance dendrite outgrowth in spinal cord neurons after SCI. Knocking down of SOCS3 in spinal cord neurons with Lenti-shSOCS3 enhanced complete SCI-induced P-STAT3 Tyr705. Immunohistochemical analysis showed that complete SCI induced a significant reduction of microtubule association protein 2 (MAP-2) positive (MAP-2+) dendrites in the gray and white matter at 1 and 4 weeks after injury. The SCI-induced reduction of MAP-2+ dendrites was inhibited by infection with Lenti-shSOCS3 in areas both rostral and caudal to the lesion at 1 and 4 weeks after complete SCI. Furthermore, shSOCS3 treatment enhanced up-regulation of growth associated protein-43 (GAP-43) expression, which co-localized with MAP-2+ dendrites in white matters and MAP-2+ cell bodies in gray matters, indicating Lenti-shSOCS3 may induce dendritic regeneration after SCI. Moreover, we demonstrated that Lenti-shSOCS3 decreased SCI-induced demyelination in white matter of spinal cord both rostral and caudal to the injury site 1 week post-injury, but not rostral to the injury at 4 weeks. Collectively, these results suggest that SOCS3 has negatively regulatory

effects on dendritic regeneration, at least in part by inhibition of dendritic loss, through negative regulation of STAT3 signaling after SCI.

Disclosures: **K. Park:** None. **C. Lin:** None. **K. Li:** None. **Y. Lee:** None.

Poster

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Support: NIH/NINDS R01 NS073584

NIH/NIGMS P30 GM103507

Title: Differential activation and effects of the PERK, ATF6, and IRE1 arms of the ER stress response after spinal cord injury

Authors: ***S. R. WHITTEMORE**, S. MULLINS, K. R. ANDRES, A. S. RIEGLER, M. HETMAN, S. SARASWAT OHRI;
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Abstract: Spinal cord injury (SCI) initiates a cascade of secondary cell death mechanisms in most resident cells. These pathophysiologic responses have been shown in non-CNS cells to initiate the endoplasmic reticulum stress response (ERSR). We addressed the extent to which and in what cell types, the ERSR was initiated after contusive thoracic SCI in adult mice. All three signaling branches are rapidly up regulated as early as 6 hours post-SCI and remained elevated until 72 hours post-SCI as detected by both PCR and immunohistochemistry. CHOP expression was observed in neurons and oligodendrocytes, but not in astrocytes at 72 hours post-SCI. In CHOP null mice, the ERSR was attenuated and hindlimb locomotor function significantly improved. At both acute (72 hours) and chronic (6 weeks) times after SCI, oligodendrocytes were significantly spared. Thus, blocking the pro-apoptotic aspects of the ERSR in oligodendrocytes was one mechanism underlying behavioral recovery. To explore if pharmacological enhancement of the homeostatic arm of PERK signaling was similarly therapeutically protective after SCI, mice were treated with salubrinal, which inhibits the dephosphorylation of eIF2α by both PPP1R15A/GADD34 and PPP1R15B/CReP, the stress-inducible and constitutive eIF2α phosphatases, respectively. Salubrinal treatment resulted in similar ERSR attenuation, oligodendrocyte sparing, and locomotor recovery. Guanabenz, an

FDA approved, specific inhibitor of PPP1R15A/GADD34 promoted the survival of OPCs treated with tunicamycin *in vitro* and enhanced eIF2α phosphorylation after SCI. However, guanabenz treatment of wild type mice after SCI (or SCI in GADD34 null mice) showed differential attenuation of the ERSR and no locomotor improvement. ATF6 null mice also show attenuation of the ERSR after SCI, but no enhanced recovery. Conditional deletion of XBP1, an effector downstream of IRE1, in oligodendrocytes did not enhance functional recovery after SCI. The pro-homeostatic aspects of the ERSR appear to be the most attractive therapeutic target after CNS injury.

Disclosures: S.R. Whittemore: None. **S. Mullins:** None. **K.R. Andres:** None. **A.S. Riegler:** None. **M. Hetman:** None. **S. Saraswat Ohri:** None.

Poster

590. Spinal Cord Injury: Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 590.20/H13

Topic: C.10. Trauma

Support: NS073584

GM103507

Title: Role of autophagy in oligodendrocyte survival and functional recovery after thoracic SCI

Authors: *S. O. SARASWAT, A. BANKSTON, A. MULLINS, A. METZ, M. HETMAN, S. WHITTEMORE;
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Abstract: Autophagy is a basic catabolic mechanism that involves cell degradation of unnecessary or dysfunctional cellular components through the action of lysosomes. During this process, targeted cytoplasmic constituents are isolated from the rest of the cell within autophagosome, a double-membraned vesicle. Autophagosomes mature by fusing with the lysosome to form the autolysosome, leading to degradation of the inner membrane and cargo and recycling of the products to the cytoplasm. Autophagosome complex formation involves the PI3K Vps34, Beclin-1, Ambra1 and two ubiquitin-like conjugation systems: 1) conjugates of Atg12 ligated to Atg5 to form oligomers with Atg16L and 2) lipidation of cleaved LC3 (Atg8) by addition of phosphatidyl ethanolamine, converting LC3-I to LC3-II. Induction of autophagy has been observed in response to starvation, endoplasmic reticulum (ER) stress, and apoptosis.

Recent data showed that acute manipulation of the ER stress response (ERSR) pathway after thoracic contusive spinal cord injury (SCI) improved functional recovery and identified oligodendrocytes as uniquely sensitive to ERSR. Interestingly, ERSR genes remain elevated at the injury epicenter for at least 6 weeks. Our preliminary data indicate that: 1) the mRNA levels of key autophagy markers, Atg5, Beclin1 and Ambra1 are dysregulated acutely after T9 contusive SCI, remain disrupted at least until 6 weeks and correlate with the ERSR data. 2) The levels of LC3, an unequivocal marker of autophagy, remain elevated for at least 2 weeks post-injury. 3) Blocking autophagy in oligodendrocyte precursor cells (OPCs) exposed to ER stress resulted in enhanced survival. 4) Differentiated oligodendrocytes (OLs) show enhanced autophagic flux, especially in the processes compared to OPCs. 5) Protein levels of MBP, LC3B, Atg5 and beclin1 are enriched in purified myelin fractions of contused day 8 post-SCI tissue suggesting autophagy is active in remyelination after SCI. These preliminary data suggest that the complex autophagic mechanism is distinct in OPCs vs. OLs and that the timing of modulating autophagy after SCI will be critical. Importantly, the results identify a window(s) of opportunity to manipulate autophagy for a therapeutic benefit after SCI. Ongoing studies are examining the effects of genetically and pharmacologically manipulating autophagy after SCI. Supported by NS073584 and GM103507.

Disclosures: S.O. Saraswat: None. **A. Bankston:** None. **A. Mullins:** None. **A. Metz:** None. **M. Hetman:** None. **S. Whittemore:** None.

Poster

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Topic: C.10. Trauma

Support: NS045734

NS073584

GM103507

Title: Crosstalk between endoplasmic reticulum stress response and autophagy pathways in CNS endothelial cell survival

Authors: *S. A. MYERS[1], A. E. RIEGLER[2], K. R. ANDRES[2], S. SARASWAT-OHRI[2], T. HAGG[3], S. R. WHITTEMORE[2];

[1]Univ. Louisville, Louisville, KY; [2]Univ. of Louisville, Louisville, KY; [3]East Tennessee State Univ., Johnson City, TN

Abstract: Following stress, endothelial cells (ECs) initiate the unfolded protein response (UPR) after endoplasmic reticulum (ER) stress sensors (XBP-1, PERK, and ATF6α) detect a high unfolded/misfolded protein to ER chaperone ratio. These stress sensors also initiate macroautophagic responses by promoting autophagosome vesicle nucleation and elongation. ER stress within ECs contributes to many diseases, including hypertension, atherosclerosis, diabetes, and bleeding disorders. We previously showed that genetic deletion of the ER stress pro-apoptotic protein C/EBP homologous protein (CHOP) improved vascular sparing and enhanced locomotor recovery following moderate spinal cord injury. We hypothesized that inhibiting signals upstream of CHOP may similarly reduce ER stress-induced apoptosis and improve sparing of primary, CNS-derived ECs. Deletion of the eIF2α kinase PERK, however, actually increased CHOP expression and apoptosis. This increase appears, in part, due to a compensatory overexpression of XBP-1 signaling. Deletion of the ER associated degradation (ERAD) protein ATF6α led to similar increases in ER stress-induced cell death, in part due to a compensatory overexpression of XBP-1 and PERK mRNA. Targeted deletion of XBP-1 had little long-term effects on ER stress-induced apoptosis. We further observed that when ER stress-induced autophagy was blocked by PI3 kinase inhibition, the extent of ER-localized misfolded proteins as well as CHOP expression was reduced, suggesting that inhibition of autophagy further reduces ER stress responses in ECs. These data implicate signals regulating both ER stress and macroautophagy as potential targets for therapeutic intervention within diseases exacerbated by vascular dysfunction. Future experiments will explore whether these interactions are synergistic. Supported by NS045734, NS073584, and GM103507.

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Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Support: NS073584

GM103507

Title: Inhibition of RNA-polymerase-1 protects oligodendrocytes against endoplasmic reticulum stress

Authors: *E. KILANCZYK;
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Abstract: Inhibition of RNA-polymerase-1 protects oligodendrocytes against endoplasmic reticulum stress Ewa Kilanczyk[1] Kariena R Andres[1], Scott R Whittemore[1,3] and Michal Hetman[1,2] [1]Kentucky Spinal Cord Injury Research Center and the Departments of Neurological Surgery, [2]Pharmacology&Toxicology and [3] Anatomical Science & Neurobiology, University of Louisville, Louisville, KY Recent work has documented that the conserved ER stress response (ERSR) is activated after contusive SCI. Genetic or pharmacological modification of the ERSR protects white matter, prevents oligodendrocyte apoptosis and improves functional recovery after trauma. The ribosome is the nexus of protein synthesis. Ribosomal biogenesis takes place in the nucleolus where RNA polymerase I (Pol1)-driven transcription of ribosomal RNA (rRNA) initiates that process. As cancer cells hijack ribosome biogenesis to fuel their growth, Pol1 became a target of novel anti-cancer drugs including the clinically tested CX-5461 or the recently identified BMH-21. Surprisingly, we found that ribosomal biogenesis is increased after moderate thoracic SCI and remains active in cultured oligodendrocytes precursor cells (OPC) that were challenged with ER stress inducers tunicamycin or thapsigargin. Importantly, transient, non-toxic inhibition of ribosomal biogenesis using CX-5461 or BMH-21 protected mouse or rat OPCs against ER stress toxicity. The protection was accompanied by enhancement of the pro-survival phosphorylation of the eIF2α and moderate modulation of ER stress-mediated inhibition of general protein synthesis. Induction of the ER stress-related killer transcription factor CHOP was unaffected by Pol1 inhibitors. Instead, these agents activated p53 whose pharmacological inhibition blocked the anti-ER stress protection. Most interestingly, *i.p.* treatment with BMH-21 inhibited ribosomal biogenesis in the mouse spinal cord and increased expression of oligodendrocyte markers following SCI. These findings suggest that the nucleolar disruption and the subsequent activation of p53 support OPC and/or oligodendrocyte survival under conditions of ER stress. Supported by NS073584, GM103507, and the Kentucky Spinal Cord and Head Injury Research Trust (SRW,MH).

Disclosures: E. Kilanczyk: None.

Poster

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Support: NS073584

GM103507

Kentucky Spinal Cord and Head Injury Research Trust

Title: Autophagy regulates the final stages of CNS myelination

Authors: ***A. N. BANKSTON**, A. E. METZ, R. M. HOWARD, S. R. WHITTEMORE; Kentucky Spinal Cord Injury Res. Ctr., Univ. of Louisville, Louisville, KY

Abstract: Myelination of the central nervous system (CNS) is a tightly regulated process. Oligodendrocyte precursor cells (OPCs) proliferate and migrate to target axons, where they mature to myelinating oligodendrocytes (OL), the sole providers of CNS myelin. Many factors have been identified that regulate OL differentiation and myelination. However, few factors have been found that act specifically in myelin formation, and the mechanisms regulating myelin sheath wrapping and compaction are poorly understood. Here, we present evidence that autophagy, the targeted isolation of cytoplasm and organelles by the double-membrane autophagosome for lysosomal degradation, regulates myelin formation in mature OLs. Autophagy is critical for cell homeostasis, but recent evidence has shown that autophagy regulates OL survival and differentiation and morphogenesis of neurons and astrocytes in the brain. Our data show: 1) increased autophagosome formation, trafficking, and autophagic flux, especially in OL processes, during late stages of OL differentiation and myelin wrapping, 2) autophagy regulatory proteins co-localization with markers of the OL lineage during myelin development, 3) detection of key autophagy regulatory proteins in enriched myelin fractions from corpus callosum (CC) at the peak of myelination and immunostaining of DRG co-cultures, 4) time-lapse imaging demonstrates autophagosome movement from myelin to the OL soma in DRG co-cultures, 5) autophagy inhibition blocked and autophagy stimulation enhanced myelination, 6) increased autophagy activation during remyelination after cuprizone-induced demyelination. These results provide insight into novel functions of autophagy in OL and myelin development and identify autophagy as an attractive target to both promote OL survival and subsequent myelin repair after injury.

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Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Title: Two PTP receptors for CSPG inhibitors use convergent and divergent signaling pathways in neurons

Authors: *Y. OHTAKE[1], D. WONG[1], P. M. ABDUL-MUNEER[1], M. E. SELZER[2], S. LI[1]; [2]Neurol., [1]SHPRC, Temple Univ. Sch. of Med., Philadelphia, PA

Abstract: The extracellular matrix molecule chondroitin sulfate proteoglycans (CSPGs) are axon growth inhibitors that are highly upregulated by reactive scar tissues, forming a potent chemical barrier to axon regeneration after CNS injuries. CSPGs may mediate suppression of axon growth by several mechanisms, including binding and activating functional transmembrane receptors, sterically hindering growth-promoting adhesion molecules and facilitating inhibitory effects of chemo-repulsive molecules. In particular, recent studies support that the receptor protein tyrosine phosphatase σ (PTPσ) and its subfamily member leukocyte common antigen related (LAR) phosphatase act as the transmembrane receptors that mediate the growth inhibiting effects of CSPGs. Transgenic or pharmacological inhibition of either PTPσ or LAR receptor promotes significant regrowth of descending or ascending axons into and beyond scar tissues and functional recovery in adult rodents with spinal cord injury. However, the molecular basis for requirement of two similar PTP receptors by neurons is not clear, including the downstream signals that mediate the effects of these two receptors. In the present study, we performed the parallel *in vitro* experiments in cultures of the neuronal cell line N2A overexpressed with PTPσ or LAR and compared their intracellular downstream signaling pathways following CSPG stimulation. Our results indicate that PTPσ and LAR employ some signaling pathways in common, including RhoA, Akt, Erk and MAP1B, but also use distinct signaling pathways to mediate CSPG function. Activation of PTPσ by purified CSPGs selectively inactivated CRMP2, APC, S6 kinase and CREB. In contrast, activation of LAR by CSPGs selectively activated PKCζ and inactivated cofilin and LKB1. We thus proposed a model of the CSPG downstream pathways based on our experimental findings. The presence of both convergent and divergent downstream signaling pathways of PTPσ and LAR suggests that blocking both PTP receptors may have synergistic therapeutic effects in overcoming CSPG inhibitory effects of neuronal growth.

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Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Support: the Chinese National Natural Science Foundation Grant NO.81330028

Title: The effects of a nt-3 persistent delivery gelatin sponge scaffold on mscs growth *in vitro* and spinal cord tissue regeneration in rats and canines

Authors: ***G. LI**[1], Y.-S. ZENG[2];
[2]Histology and Embryology,, [1]Sun Yat-Sen Univ., Guangdong, China

Abstract: Neurotrophin-3 (NT-3) plays an essential role in the development of nervous system. Our previous studies have demonstrated that Schwann cells overexpressing NT-3 could support sufficient nutrition for constituting an adult stem cell-derived neural network. In the present study, we evaluated the physiological effects of a new-developed NT-3/fibroin coated gelatin sponge (NF-GS) scaffold to establish a controlled artificial release system that may serve as a novel therapy of spinal cord injury (SCI). A lyophilization technique was used to immobilize NT-3/fibroin complex to gelatin sponge scaffold. The physical, chemical and physiological properties of the NF-GS scaffolds were tested by seeding bone marrow-derived mesenchymal stem cells (MSCs) *in vitro*. Then, NF-GS scaffolds were implanted into the injury site of rat and canine spinal cords to directly investigate the therapeutical effects *in vivo*. *In vitro* release test showed that the NF-GS was capable to generate a sustainable NT-3 release in 28 days. A 7-days culture indicated that MSCs could maintain high cell activity as well as excellent cell distribution and morphous. *In vivo* study showed that the total concentration of NT-3 in rat host spinal tissue was much higher in the NF-GS group than the control group 4 weeks after graft. Additionally, cavity areas within the injury/graft site of spinal cord were significantly reduced due to tissue regeneration and axon extension with myelinization in rats and canines. The results suggest that we establish a bioactive scaffold to persistently release NT-3 *in vitro* and *in vivo*. This scaffold will greatly facilitate our future experiments loading or attracting stem cells for repairing SCI.

Disclosures: **G. Li:** None. **Y. Zeng:** None.

Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Support: SC SCIRF

USC SOM RDF

Title: microRNA mediated augmentation of therapeutic effects of synthetic bororetinoid in mono-culture and co-culture models of spinal cord injury

Authors: *S. K. RAY[1], M. CHAKRABARTI[1], B. C. DAS[2];
[1]Dept Patho Micro & Immuno, Univ. SC Sch. Med., Columbia, SC; [2]Kansas Univ. Med. Ctr., Kansas City, KS

Abstract: Spinal cord injury (SCI) is a complex neurological problem that begins with a rapid mechanical injury or breakup of the spine. A severe SCI can cause paralysis and even death. Primary injury to the spinal cord initiates progressive secondary injury processes such as calcium overload causing cell death that spans over time to the rostral and caudal regions. The only recommended therapy for SCI is methylprednisolone (MP) that shows poor efficacy and its use in SCI is now highly controversial. So, new therapeutic agents for targeting secondary injury pathways must be developed for neuroprotection in spinal cord in the SCI patients. Recent investigations show that retinoids at lower doses are promising therapeutic agents for inhibiting apoptosis, augmenting autophagy, and reducing expression of various pro-inflammatory cytokines. In current investigation, we examined therapeutic efficacy of our synthetic bororetinoids in cell culture models of SCI. We found that all-trans retinoic acid, a natural retionoid, at a low dose (1 μM) caused significant cell death while each of our synthetic bororetinoids (BIT-5, BIT-6, and BIT-7) even at 10 μM did not induce significant cell death in ventral spinal cord 4.1 (VSC4.1) motoneurons. In a mono-culture model of SCI (exposure of VSC4.1 motoneurons to 200 nM A23187, a calcium ionophore (CI), for 24 h) induced significant neuronal death but 10 μM BIT-5 most significantly prevented the CI induced neuronal death. Our real-time quantitative reverse transcription-polymerase chain reaction (qRT-PCR) experiments indicated decreases in expression of six neuroprotective microRNAs (miRs) such as miR-34a, miR-138, miR-184, miR-96, miR-98, and miR-133b in VSC4.1 motoneurons after CI insult. Notably, expression of miR-96 was most significantly decreased in the CI insulted motoneurons. So, we hypothesized that overexpression of miR-96 could augment

therapeutic efficacy of BIT-5 in cell culture models of SCI. Our cellular and molecular results indicated that induction of autophagy, a survival mechanism, in CI exposed VSC4.1 motoneurons was suppressed due to treatment with MP but increased due to treatment with combination of miR-96 and BIT-5. Also, in a co-culture model of SCI (VSC4.1 motoneurons and C6 astroglial cells exposed to CI), we found that combination of miR-96 and BIT-5 was the most effective treatment in preventing apoptosis, promoting autophagy, and inhibiting pro-inflammatory molecules in both neuronal and astroglial cells. Collectively, our studies demonstrated that miR-96 augmented therapeutic effects of BIT-5 in both mono-culture and co-culture models of SCI. This work was supported in part by SC SCIRF and USC SOM RDF.

Disclosures: **S.K. Ray:** None. **M. Chakrabarti:** None. **B.C. Das:** None.

Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Support: DOD Grant W81XWH-11-1-0707

NIH Grant NS069765

Title: Differential intensity-dependent effects of magnetic stimulation on the longest neurites and shorter dendrites in neuroscreen-1 cells

Authors: *C.-Y. LIN[1], K. LIN[1], V. LIN[2], Y.-S. LEE[1];
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Abstract: Magnetic stimulation (MS) is a potential treatment for neuropsychiatric disorders. This study investigates if MS-regulated neuronal activity can translate to specific changes in neuronal arborization and thus regulate synaptic activity and function. To test our hypotheses, we examined the effects of MS on neurite growth of Neuroscreen-1 (NS-1) cells over pulse frequencies of 1, 5 and 10 Hz at field intensities controlled by machine output (MO). Cells were treated with either 30% or 40% MO and received either maximal or minimal MS-induced current density. Due to the nature of circular MS coils, the center region of the gridded coverslip (zone 1) received minimal (~5%) electromagnetic current density while the remaining area (zone 2) received maximal (~95%) current density. Plated NS-1 cells were exposed to MS twice per day for 3 days and then evaluated for length and number of neurites and expression of brain-derived

neurotrophic factor (BDNF). We show that MS dramatically affects the growth of the longest neurites (axon-like) but does not significantly affect the growth of shorter neurites (dendrite-like). Also, MS-induced changes in the longest neurite growth were most evident in zone 1, but not in zone 2. MS effects were intensity-dependent and were most evident in the bolstering of the longest neurite outgrowth, mainly seen in the 10 Hz MS group. Furthermore, we found that MS-increased BDNF expression and secretion was also frequency-dependent. Taken together, our results show that MS exerts distinct effects when different frequencies and intensities are applied to the neuritic compartments (longest neurite versus shorter dendrite(s)) of NS-1 cells. These findings support the concept that MS increases BDNF expression and signaling, which sculpts longest neurite arborization and connectivity by which neuronal activity is regulated. Understanding the mechanisms underlying MS is crucial for efficiently incorporating its use into potential therapeutic strategies.

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Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Topic: C.10. Trauma

Title: Safety assessment of NSCs induced from human PBMC-derived iPS cells

Authors: *K. SUGAI[1,2], T. SHOFUDA[3], R. FUKUZAWA[5], H. FUKUSUMI[4], M. ISODA[2], S. OHTA[2], J. KOHYAMA[2], A. IWANAMI[1], M. MATSUMOTO[1], Y. KANEMURA[3,4], M. NAKAMURA[1], H. OKANO[2];
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Abstract: [Purpose] Transplantation of neural stem cells (NSCs) is now considered to be a promising treatment for various central nervous system disorders. In countries where fetal NSCs are not allowed to use due to ethical issues, iPS cells are a potential cell source of NSCs for cell therapy. Especially in Japan, an iPS cell bank is planned to be established from peripheral blood mononuclear cells (PBMCs). To apply these cells to clinic, we developed three Good Manufacturing Practice (GMP) grade protocols to induce PBMC-derived iPSCs into NSCs. We compared its characteristics *in vitro*, and *in vivo*, and investigated useful markers to distinguish

safe NSCs for clinical use. [Methods] Two feeder-free iPSC lines established from human adult PBMCs were used (1210B2, 1231A3). First, the karyotype of the iPSCs was checked. Next, the iPSCs were induced into NS/PCs by three different protocols: (ProA, B, and C). Neural phenotypes, multipotency, and cellular heterogeneity of induced NS/PCs were evaluated by immunocytochemistry, qRT-PCR, and flow cytometry (FACS). Microarray analysis was also performed to compare the quality of each NSC lines. To assess cellular behavior *in vivo*, intracranial or spinal xenograft models were used. For intracranial xenograft models, 1x10^6 NS/PCs were injected into each side of the striatum of intact NOG mice. For spinal xenograft models, 5x10^5 NSCs were transplanted into the spinal cord of NOD/SCID mice 9 days after contusion injury. Their histologically examined 13-26 weeks after transplantation to see the *in vivo* characteristics of the transplants. [Results] *In vitro*, karyotype analysis revealed that the frequency of copy number variation (CNV) was higher in 1231A3-iPSCs than in 1210B2-iPSCs. All three neural induction protocols had the potential to induce PBMC-derived iPS cells into NSCs. FACS analysis revealed that there were more subtypes of neural crest stem cells (NCSCs) in ProC-NSCs. Microarray clustering analysis also showed that ProA-NSCs and ProB-NSCs were more similar to fetal derived-NSCs than ProC-NSCs. *In vivo*, 1210B2-ProA-NSCs had the best integration to the host brain and also to the spinal cord. 1210B2-ProB-NSCs had a tendency to leak to the subdural space when transplanted into the spinal cord. 1231A3-ProA-NSCs revealed massive growth both in the brain and spinal cord. Bone formation was observed from 1210B2-ProC-NSCs 6 months after transplantation to the spinal cord. [Conclusion] 1210B2-ProA-NSCs had the best quality *in vitro* and *in vivo*. All of the analyses performed in this study were important. Further study should be performed to determine *in vitro* markers to set effective criteria to certify safe and useful NSCs.

Disclosures: **K. Sugai:** None. **T. Shofuda:** None. **R. Fukuzawa:** None. **H. Fukusumi:** None. **M. Isoda:** None. **S. Ohta:** None. **J. Kohyama:** None. **A. Iwanami:** None. **M. Matsumoto:** None. **Y. Kanemura:** None. **M. Nakamura:** None. **H. Okano:** None.

Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Support: TWU Department of Biology

The Southeast Missouri State University Department of Physics and Engineering Physics

TWU Research Enhancement Program

Title: Pharmacological inhibition of clathrin mediated endocytosis and the effect of magnetic nanoparticles in the morphology of primary neurons

Authors: *R. AMMASSAM VEETTIL[1], T. MCALLISTER[2], S. GHOSH[2], S. SEBASTIAN[1], D. HYNDS[1];
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Abstract: Traumatic central nervous system (CNS) injury leads to neuronal damage and results in varying levels of functional impairment. Nanomaterial-based drug delivery systems provide potential for axon regeneration from specific neurons by crossing blood brain barrier. From our previous experiments we found that -NH2 and -COOH surface functionalized nanoparticles were internalized through clathrin mediated endocytosis. In the present study we are using clathrin inhibitors to block the clathrin mediated endocytosis. This would confirm the definite mechanism through which the nanoparticles are endocytosed. We also used magnetic nanoparticles to study the time and dose dependant effects on neurite outgrowth in primary dorsal root ganglion (DRG) neurons from embryonic chick. We are treating dissociated DRG with different concentrations of magnetic nanoparticle for 72 hours. We will then look for any change in the number of neurites, branches and neurite length. We except to see no effect on the morphology of neurons after magnetic nanoparticle treatment. Together, these results will test the feasibility of MNP nanocarriers for targeted drug delivery to encourage axon regeneration following nervous system damage.

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Poster

590. Spinal Cord Injury: Therapeutic Strategies

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Title: Transdifferentiation of human keratinocytes into oligodendrocyte progenitors

Authors: *P. MOHAMMAD GHARIBANI[1], C. KERR[2], S. CHUA[3], A. ALL[1,3];
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Abstract: Recent reports show that somatic cells can be directly converted to other mature cell types by using combined expression of defined factors. Here for the first time, we show that the same strategy can be applied to human keratinocytes to be directly converted into induced-human oligodendrocyte progenitors (i-hOPs). Epigenetically unstable state was developed using the single transcriptional factor Sox2 in human foreskin fibroblasts for 1 week. Then, i-hOP induction was carried out by using FGF2, EGF and PDGF for 2 weeks. We successfully derived these cells and not only expanded them for 3 months but also, extensively characterized them by Immunocytochemistry (ICC), Fluorescence activated cell sorting (FACS) and Western Blot (WB). Interestingly, our *in vitro* experiment revealed that these i-hOPs expressed oligodendrocyte (OL) markers even after 3 months expansion. We stained the i-hOP cells with O4 and NG2 antibodies for the FACS experiment. The Oligodendrocyte marker O4 reacts with late OL progenitors as well as OLs that have entered terminal differentiation, while NG2 (Neural/glial antigen 2) is present only on the surface of developing oligodendrocyte precursor cells. Analytical FACS results showed that almost 80% of the i-hOPs express O4, while only 20% of the i-hOPs express NG2. This data reveals that our i-hOPs are mostly oligodendrocyte progenitor cells. ICC of i-hOPs has also confirmed that more than 70% of the i-hOPs are O4 positive. In addition, we have also shown that these cells express O1, a late marker of OL. WB has shown that these i-hOP cells do not express nestin, a marker of stemness. Olig-1 is a bHLH transcription factor that is expressed by oligodendrocytes in the brain where it promotes OL formation and maturation. WB on our i-hOPs showed Olig-1 expression. In additional tests, the level of expression of MAG (Myelin Associated Glycoprotein) and MOG (Myelin Oligodendrocyte Glycoprotein) in i-hOPs after 3 months showed the potential of these cells to carry out myelination *in vitro*. Most importantly, the absence of K5, a marker of keratinocytes, in our i-hOP cells revealed that the proposed direct conversion of foreskin fibroblasts into OPs was successfully done without keratinocyte differentiation. This is a significant milestone, since these i-hOPs were derived directly from the transformation of adult human fibroblasts without an intermediate pluripotent state, which helps to avoid all limitations of using iPS derived cells. At the same time, these i-hOP cells will be patient-specific and optimal for a time-sensitive pathology like spinal cord injury, since these cells can be obtained in a shorter time with a higher yield and purity.

Disclosures: P. Mohammad Gharibani: None. **C. Kerr:** None. **S. Chua:** None. **A. All:** None.

Poster

591. Cell Death Mechanisms: Apoptosis and Mitochondria

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 591.01/H24

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Eugenol exhibits anxiolytic activity in diabetic encephalopathic rats

Authors: *J. KHAN, D. GARABADU, S. KRISHNAMURTHY;
Indian Inst. of Technol. (BHU), Varanasi, India

Abstract: Diabetic encephalopathy is considered as one of the most prevailing complication in type-2 diabetic population. Several synthetic drugs such as thiazolidinediones, dipeptidyl peptidase 4 (DPP-4) inhibitors, biguanides are used for type-2 diabetes mellitus (T2DM)-induced encephalopathic condition. However, their use is limited because several adverse effects such as hypoglycemia, weight gain and gastrointestinal symptoms are associated with them. Therefore, there is need to develop drugs for management of T2DM-induced neurological complications. Eugenol is a phenylpropanoid with several pharmacological activities including anti-stress activity. Therefore, we evaluated the neuroprotective effect of eugenol in T2DM-induced diabetic encephalopathy. In the present study, streptozotocine (45 mg/kg, i.p.) and nicotinamide (110 mg/kg, i.p.), at a time lag of 15 min, were injected to induced T2DM in male rats. After confirmation of diabetes in terms of plasma glucose level on day-7 after streptozotocine injection, the animals were treated with vehicle or metformin (25 mg/kg, p.o.) or eugenol (12.5, 25.0 and 50.0 mg/kg, p.o.) for four consecutive weeks. On the last day of the experiment (i.e. day-31), eugenol (50 mg/kg) exhibited anxiolytic activity in terms of increase in the T2DM-induced decrease in percentage in the entries and time spent into open arm in EPM test. The highest dose of eugenol also mitigated anxiety in diabetic encephalopathic rats in hole-board test in terms of increase and decrease in the number of head-dip and edge-sniff. Eugenol (50 mg/kg) attenuated hyperglycemia and hyperinsulinemia along with the improvement in insulin resistance and beta-cell function in T2DM-induced diabetic encephalopathic rats. Eugenol at the highest dose level also reversed the T2DM-induced mitochondrial dysfunction, integrity and oxidative stress (level of lipid peroxidation and activities of superoxide dismutase and catalase) in the amygdala. Hence, eugenol could be a potential candidate for the management of T2DM-induced diabetic encephalopathy.

Disclosures: J. Khan: None. **D. Garabadu:** None. **S. Krishnamurthy:** None.

Poster

591. Cell Death Mechanisms: Apoptosis and Mitochondria

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 591.02/H25

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: CSIR-SRF Grant 9/13 (366)/2011-EMR-I

Title: Metformin exhibits anxiolytic activity in experimental type-2 diabetic rats

Authors: *D. GARABADU, S. KRISHNAMURTHY;
Indian Inst. of Technol. (Banaras Hindu University), Varanasi, India

Abstract: Type-2 diabetes mellitus (T2DM) is mostly associated with several peripheral as well as central complications including anxiety. It has also been reported that the therapeutic regimen gains critical attention when there is a comorbid condition of T2DM and anxiety. Hence, it is necessary to investigate the pathophysiology of anxiety in T2DM condition. The insulin signaling glucose utilization pathway i.e., PI3K/Akt/GLUT-4 is deranged in T2DM condition along with mitochondrial dysfunction. However, there is no report on the cross-talk between PI3K/Akt/GLUT-4 signaling pathway and mitochondrial dysfunction in such comorbid condition. Therefore, the present study evaluated the relationship between PI3K/Akt/GLUT-4 signaling and mitochondrial dysfunction in T2DM-induced anxiety animals using metformin as standard drug. T2DM was induced in male rats by a single injection of nicotinamide (110 mg/kg, i.p.) and streptozotocine (45 mg/kg, i.p.) with a time lag of 15 min (day-1). Metformin (25 mg/kg, p.o.) was administered once daily for seven consecutive days from day-7. Metformin on day-13 exhibited anxiolytic activity by reversing the T2DM-induced increase in ambulation, rearing and percentage of time spent in the center during open-field test, decrease and increase in the number of head-dip and edge-sniff respectively and decrease in the ratio of head-dip to edge-sniff during hole-board test, and decrease in the percentage entries and time spent into open arm during elevated-plus maze test. Metformin showed anti-diabetic activity by mitigating the disturbed glucose homeostasis, beta-cell dysfunction and insulin resistance in T2DM rats. Metformin increased phosphorylated Akt level and translocation of GLUT-4 into the plasma membrane in amygdale of T2DM rats. Moreover, it mitigated T2DM-induced alterations in loss of mitochondrial integrity (mitochondrial membrane potential and level of expression of cytoplasmic cytochrome-C) and oxidative stress (lipid peroxidation) in amygdala. These observations suggest that there could be a direct relationship between derangement of PI3K/Akt/GLUT-4 signaling pathway and mitochondrial dysfunction in amygdale of T2DM-induced anxiety. Metformin was able to ameliorate these alterations in amygdale of these animals. Thus, metformin could be a therapeutic option in the management of co-occurring condition of T2DM and anxiety.

Disclosures: D. Garabadu: None. **S. Krishnamurthy:** None.

Poster

591. Cell Death Mechanisms: Apoptosis and Mitochondria

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 591.03/H26

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Bio & Medical Technology Development Program of National Research Foundation of Korea (NRF) grant (No.2012M3A9C6049935)

DGIST Convergence Science Center Program (14-BD-04) of the Ministry of Science

Title: Valosin-containing protein (VCP)/ p97 is a key mediator between autophagic cell death and apoptosis in adult hippocampal neural stem cells following insulin withdrawal

Authors: *B. YEO, C. HONG, S. JUNG, H. WOO, S.-W. YU;
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Abstract: Programmed cell death (PCD) plays essential roles in regulation of survival and function of neural stem cells (NSCs). Abnormal regulation of this process is associated with aging and neurodegenerative diseases. However, the mechanisms underlying the PCD of NSCs remain largely unknown. Therefore, understanding the mechanism of PCD in NSCs is crucial for exploring therapeutic strategy for the treatment of neurodegenerative diseases. We have previously reported that adult rat hippocampal neural stem (HCN) cells undergo autophagic cell death (ACD) following insulin withdrawal without apoptotic signs despite their normal apoptotic capabilities. It is unknown how interconnection between ACD and apoptosis is mediated in insulin-deprived HCN cells. Valosin-containing protein (VCP) is known to be essential for autophagosome maturation in mammalian cells. In this study, we report that VCP regulates the rate of autophagic flux in HCN cells following insulin withdrawal, suggesting the novel roles of VCP at other steps of autophagy as well as maturation. Particularly, VCP is expressed abundantly in HCN cells compared to hippocampal tissue and neurons. Pharmacological and genetic inhibition of VCP significantly decreased ACD and autophagy markers, while apoptotic cell death was induced in insulin-depleted HCN cells. Taken together, these data demonstrate that VCP may play an essential role in completion of ACD and mediation of crosstalk between ACD and apoptosis in HCN cells following insulin withdrawal. Elucidating the mechanism by which VCP regulates the crosstalk of ACD and apoptosis will contribute to understanding the molecular mechanism of PCD in NSCs.

Disclosures: **B. Yeo:** None. **C. Hong:** None. **S. Jung:** None. **H. Woo:** None. **S. Yu:** None.

Poster

591. Cell Death Mechanisms: Apoptosis and Mitochondria

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 591.04/H27

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Title: Dual Leucine-Zipper Kinase (DLK) dependent regulation of the Integrated Stress Response contributes to neurodegenerative and neuroregenerative responses

Authors: *M. LARHAMMAR[1], S. HUNTWORK-RODRIGUEZ[1], A. SENGUPTA GHOSH[1], Z. JIANG[1], H. SOLANOY[1], J. EASTHAM-ANDERSON[1], J. S. KAMINKER[2], J. W. LEWCOCK[1], T. A. WATKINS[3,1];
[1]Neurosci., [2]Bioinformatics, [3]Phamacodynamic Biomarkers within Develop. Sci., Genentech Inc, South San Francisco, CA

Abstract: Characterization of the cellular pathways activated upon neuronal stress is essential for our understanding of the underlying mechanisms contributing to neurodegenerative diseases. Axonal damage triggers both regenerative and apoptotic responses, yet the molecular pathways mediating these divergent outcomes remain elusive. The ISR can be engaged by a variety of insults, from oxidative stress to viral infection, and has recently emerged as a putative mediator in neurological conditions. In the present study we employed a combination of molecular biology techniques, pharmacology and nerve injury models in transgenic mice to show that the Integrated Stress Response (ISR) is activated upon neuronal stress and influences transcriptional and functional outcomes *in vitro* and *in vivo*. We observed activation of the ISR-associated protein kinase R (PKR)-like endoplasmic reticulum (ER) kinase (PERK, EIF2AK3) and up-regulation of Activating Transcription Factor-4 (ATF4) protein following sciatic and optic nerve injuries in mice. Disruption of either ATF4 or PERK enhances axon regrowth from adult sensory neurons *in vitro*, and neuronal-specific deletion of PERK in mice improves survival of retinal neurons after optic nerve damage. Furthermore, we demonstrate that an essential regulator of MAP kinase neuronal stress response pathways, Dual Leucine-Zipper Kinase (DLK, MAP3K12), is also required for ISR activation and that inhibition or deletion of DLK reduces the ISR *in vitro* and *in vivo*. Taken together, our current findings imply that the ISR is a critical component of the broad DLK-mediated stress response and a significant contributor to neuronal fate, highlighting the clinical potential of targeting the ISR in disease.

Disclosures: **M. Larhammar:** A. Employment/Salary (full or part-time):; Genentech Inc. **S. Huntwork-Rodriguez:** A. Employment/Salary (full or part-time):; Genentech Inc. **A. Sengupta Ghosh:** A. Employment/Salary (full or part-time):; Genentech Inc. **Z. Jiang:** A. Employment/Salary (full or part-time):; Genentech Inc. **H. Solanoy:** A. Employment/Salary (full

or part-time):; Genentech Inc. **J. Eastham-Anderson:** A. Employment/Salary (full or part-time):; Genentech Inc. **J.S. Kaminker:** A. Employment/Salary (full or part-time):; Genentech Inc. **J.W. Lewcock:** A. Employment/Salary (full or part-time):; Genentech Inc. **T.A. Watkins:** A. Employment/Salary (full or part-time):; Genentech Inc.

Poster

591. Cell Death Mechanisms: Apoptosis and Mitochondria

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 591.05/H28

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Construction fund for key subjects of Hunan Province2013

125 Talents Foundation of the Third Xiangya Hospital of Central South University

Title: TCP and CPFO, the metabolites of CPF induce neurotoxicity in SH-SY5Y cells

Authors: *H. DAI[1], L. ZHAO[1], Y. DENG[1], J. ZHANG[2];
[1]Third Xiangya Hosp. of Central South Univ., Hunan, China; [2]Dept. of neurology, the Second Xiangya Hosp. of Central South Univ., Hunan, China

Abstract: Chlorpyrifos (CPF) is one of the most widely used organophosphate pesticides. CPF can be converted into its active neurotoxic metabolite chlorpyrifos oxon (CPFO) by cytochrome P450-dependent oxidative desulfuration. Both CPF and CPFO can be hydrolyzed to 3,5,6-trichloro-2-pyridinol (TCP) in a detoxification pathway. A large amount of research has proved that CPF exposure was associated with neurodevelopmental disorders. However, the mechanism of neurotoxicity of the metabolites remain a mystery although it has been reported that CPFO had toxic effect on nervous systems through inhibiting AchE. In present study, we tested the major metabolites TCP and CPFO in dopaminergic SH-SY5Y cells, and check their effects on cell morphology, proliferation and apoptosis and autophagy. Our results showed that both of the two metabolites could decrease SH-SY5Y cell viability,inhibit proliferation, produce excessive ROS and cause cell death via caspase-dependent pathway. Furthermore, we also found that TCP and CPFO can induce autophagy in dopaminergic cell as well as CPF. Interestingly, not only CPF but also its major two metabolites TCP and CPFO can produce excessive ROS. And further research showed only CPF itself can induce significant mitochondrial fragmentation and reduce the potential of mitochondrial membrane which suggested that there were some differences in mechanisms of neurotoxicity between CPF and its metabolites . In conclusion, metabolites TCP and CPFO is neurotoxity as well as CPF itself.

Disclosures: **H. Dai:** None. **L. Zhao:** None. **Y. Deng:** None. **J. zhang:** None.

Poster

591. Cell Death Mechanisms: Apoptosis and Mitochondria

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 591.06/H29

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NS045876

Title: Regulation of neuronal death and survival by interaction of pro and anti-death versions of Bcl-xL with the mitochondrial permeability transition pore

Authors: *H.-A. PARK[1], P. LICZNERSKI[1], P. MIRANDA[1], Y. NIU[1], S. SACCHETTI[1], K. N. ALAVIAN[2], E. A. JONAS[1];
[1]Yale Sch. of Med., New Haven, CT; [2]Imperial Col. London, London, United Kingdom

Abstract: ABT-737 is a pharmacological inhibitor of the anti-apoptotic activity of B-cell lymphoma-extra large (Bcl-xL) protein; it functions by occupying the BH3-binding domain, supporting apoptosis of cancer cells. We have shown that ABT-737 lowers neuronal metabolic efficiency by inhibiting ATP synthase activity. However, we unexpectedly found that ABT-737 protects brains from ischemic injury *in vivo*. We reported that ABT-737 inhibited formation of the pro-apoptotic, cleaved form of Bcl-xL, ΔN-Bcl-xL. In this study, we find that a high concentration of ABT-737 (1μM) blocks the effects of full length Bcl-xL but a low concentration of ABT-737 (10 nM) inhibits ΔN-Bcl-xL. We tested whether ABT-737 exerts neuroprotective properties by altering mitochondrial membrane permeability during cell death stimuli. We found that ΔN Bcl-xL levels are enhanced after glutamate-induced excitotoxicity. Pre-treatment of neurons with 1μM ABT-737 aggravated glutamate-induced death. We observed a loss of mitochondrial potential and a decline in ATP production in high ABT-737 and glutamate treated cells. In contrast, pre-treatment with 10nM ABT-737, a hundred fold lower concentration, rescued neurons from death and augmented mitochondrial potential and ATP production similarly to effects of Cyclosporine A (CsA) during glutamate challenge. Incubation of recombinant ΔN-Bcl-xL protein with isolated mitochondria significantly reduced mitochondrial potential, rescued by CsA or low ABT-737, suggesting involvement of the mitochondrial permeability transition pore. To confirm this, we depleted the c-subunit of the ATP synthase. We found that c-subunit depletion is neuroprotective against ΔN Bcl-xL accumulation in glutamate-exposed neurons. Our findings suggest that low concentrations of Bcl-xL inhibitors may promote

survival by preferentially binding to the pro-apoptotic form of Bcl-xL even as high concentrations potentiate cell death in malignant cells.

Disclosures: **H. Park:** None. **P. Licznerski:** None. **P. Miranda:** None. **Y. Niu:** None. **S. Sacchetti:** None. **K.N. Alavian:** None. **E.A. Jonas:** None.

Poster

591. Cell Death Mechanisms: Apoptosis and Mitochondria

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 591.07/H30

Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Alzheimer Association NIRG-12-241456

NIH-NIA-K01 1K01AG042500-01A1

NIH-NIGMS COBRE 5P20GM103653

NIH-NIGMS INBRE 5P20GM103446

Title: Induced Mitophagy alters localization of TDP-43

Authors: S. ITAMAN[1], K. GAN[1], S. A. DAVIS[1], *M. A. GITCHO[1,2];
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Abstract: TAR DNA binding protein (TDP-43) is a heterogeneous nuclear ribonucleoprotein (hnRNP) involved in mRNA stability and transport. While, TDP-43 is a major pathological protein in frontotemporal dementia and motor neuron disease, it also accumulates in ~50% of Alzheimer's disease (AD) cases. Besides TDP-43, dysfunctional mitochondria are one of the main underlying factors of neurodegenerative diseases. Studies have shown that overexpression of the full length TDP-43 and its C-terminal fragments activated mitophagy in a motor neuron cell line (NSC34). However, the relationship between TDP-43 and mitophagy is still unclear. We hypothesize that the induction of mitophagy causes the localization of TDP-43 from the nucleus to the mitochondria. We utilized carbonyl cyanide m-chlorophenyl hydrazone (CCCP) to disrupt the proton gradient established by the electron transport chain and subsequently are able to induce mitophagy in cells. We have found that TDP-43 localizes to the mitochondria following CCCP treatment in SH-SY5Y cells and primary cortical neurons. Further experiments are needed to delineate the role of TDP-43 in mitochondria metabolism particularly in neurodegenerative diseases.

Disclosures: **S. Itaman:** None. **K. Gan:** None. **S.A. Davis:** None. **M.A. Gitcho:** None.

Poster

591. Cell Death Mechanisms: Apoptosis and Mitochondria

Location: Hall A

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Canadian Paraplegic Association (Manitoba) to EE

Health Sciences Centre Foundation to EE

Research Manitoba Studentship (NP)

Research Manitoba Studentship (MAI)

Title: Pro-survival role of thioredoxin reductase under metabolic stress condition: interplay between autophagy and apoptosis

Authors: *N. PANDIAN[1], M. IQBAL[2], E. EFTEKHARPOUR[3];
[1]Physiol., Dept. of Physiology, Univ. of Manitoba, Winnipeg, MB, Canada; [2]Physiol., Dept. of Physiol. and Pathophysiology, Univ. of Manitoba, Winnipeg, MB, Canada; [3]Physiol. and Pathophysiology, Univ. of Manitoba, Winnipeg, MB, Canada

Abstract: Autophagy is a cellular physiologic phenomenon for normal turnover of long-term proteins and organelles. Temporary shortage of nutrients enhances autophagy through inhibition of new protein synthesis which prompts the cells to use their organelles as energy source. Upon resumption of growth material autophagy will be scaled back and cells will continue their normal activities. While short term autophagy is necessary to ensure cell survival during the stress conditions, prolonged autophagy will result in cell death. Although apoptotic cell death is the most common studied form of cell death after neurotrauma and ischemia, increasing evidence indicates the involvement of autophagy as an undergoing but less investigated form of cell damage. Rationale for studying autophagy comes from reports of functional improvements after application of autophagy inhibitors or inducers in neurotrauma or ischemia. This warrants the need for understanding the molecular mechanisms of autophagy that may lead to identification of novel therapeutic tools for CNS treatment. Oxidative stress is a major inducer of cell death. Upregulation of oxidizing agents such as oxygen and nitrogen reactive species results in oxidation of many signaling molecules and induction of autophagy or apoptosis. Thioredoxin (Trx) system is a major regulator of protein oxidation and modulator of oxidative damage. Trx is

responsible for reduction of oxidized proteins but is oxidized in this process. Thioredoxin reductase (TrxR) reduces Trx and therefore maintains the reducing capacity of the cell. TrxR is upregulated under stressful conditions and its inhibition results in cell death. The exact role of TrxR in induction of autophagy or apoptosis has not been investigated. In this study we used neuroblastoma cell line (SH-SY5Y) to study autophagy and apoptosis under normal (10% serum) and metabolic stress (0% serum) conditions. TrxR was inhibited using pharmacological inhibitors, and gene-delivery approaches. We observed that inhibition of TrxR in normal growth conditions promotes apoptosis as indicated by upregulation of caspases. This was associated with upregulation of endoplasmic reticulum (ER) stress markers IRE1, and ATF6. Serum deprivation resulted in 40% cell death that was associated with upregulation of autophagy and apoptosis markers. Serum deprived SH-SY5Y cells were several folds more sensitive to TrxR inhibition and after inhibition of TrxR, apoptosis was the prevalent form of cell death. This is the first study to investigate the role of TrxR in normal and stressed conditions. Our observations further confirm the potential therapeutic capacity of Trx system for neuroprotection.

Disclosures: **N. Pandian:** None. **M. Iqbal:** None. **E. Eftekharpour:** None.

Poster

591. Cell Death Mechanisms: Apoptosis and Mitochondria

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: Bio & Medical Technology Development Program of the NRF grant No.2012M3A9C6049935

DGIST convergence Science Center (15-BD-04) of the Ministry of Science

Title: The pro-survival role of cytosolic p53 in adult hippocampal neural stem cells

Authors: ***S. J. JUNG**, K. CHUNG, H. RYU, C. J. HONG, H. PARK, H. WOO, B. YEO, S.-W. YU;
DGIST, Daegu, Korea, Republic of

Abstract: Programmed cell death (PCD) of neural stem cells (NSCs) plays a critical role in the development and function of the central nerve system. Previously, we have reported that adult hippocampal neural stem (HCN) cells undergo autophagic cell death (ACD) following insulin withdrawal despite their intact apoptotic capabilities. Here, we demonstrate that p53 is involved

in regulation of HCN cell survivals. Basal p53 expression level is high in HCN cells, yet is degraded in response to cell death signals, such as insulin withdrawal and staurospourine (STS). Interestingly, p53 is degraded by autophagy following insulin withdrawal, whereas p53 degradation is mediated by ubiquitin proteasome system (UPS) in STS-induced apoptosis. p53 is transcriptionally inactive and localized mostly in the cytosol in HCN cells. Overexpression of p53 mutant targeted to the cytosol significantly reduced cell death after STS treatment. In summary, high expression level and cytosolic location of p53 and anti-apoptotic effects of cytosolic p53 suggest the interesting transcription-independent, pro-survival role of p53 in HCN cells. Understanding the role of p53 in response to cell death signals would help to understand the cell death mechanism of HCN cells.

Disclosures: **S.J. Jung:** None. **K. Chung:** None. **H. Ryu:** None. **C.J. Hong:** None. **H. Park:** None. **H. Woo:** None. **B. Yeo:** None. **S. Yu:** None.

Poster

591. Cell Death Mechanisms: Apoptosis and Mitochondria

Location: Hall A

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF grant from the Ministry of Education NRF-2014R1A1A2058842

Title: Amp-activated protein kinase contributes to zinc neurotoxicity in mouse cortical cultures via activation by lkb1 and induction of bim

Authors: J.-W. EOM[1], *Y.-H. KIM[2];
[1]Sejong university, Seoul, Korea, Republic of; [2]Sejong Univ., Seoul, Korea, Republic of

Abstract: Previously, we reported that zinc neurotoxicity, a key mechanism of ischemic neuronal death, was mediated by PARP over-activation and following NAD^+/ATP depletion in cortical culture. Since AMP-activated protein kinase (AMPK) can be activated by ATP depletion and some reports showed that AMPK plays a key role in excitotoxicity and ischemic neuronal death, we examined in this study, whether AMPK is involved in zinc neurotoxicity in mouse cortical neuronal cultures. Suggesting the essential role of AMPK, Compound C, a chemical inhibitor of AMPK, significantly attenuated zinc-induced neuronal death. Activation of AMPK was detected from 2 hr after the onset of 10 min exposure of mouse cortical neurons to 300 μM zinc. However, AMPK activation in zinc neurotoxicity may not be induced by the increase of intracellular AMP level, because the significant change of AMP level was detected from 4 hr

after zinc treatment in cortical neurons. As an upstream signaling pathway, we observed the involvement of Liver kinase B1 (LKB1) but not Ca^{2+}/calmodulin-dependent protein kinase kinase β (CaMKKβ). Although STO-609, a chemical inhibitor of CaMKKβ, significantly attenuated zinc neurotoxicity, zinc-induced AMPK activation was not affected by STO-609, suggesting the non-mediation by CaMKKβ of AMPK activation. In the case of LKB1, knock-down using the specific siRNA for LKB1 significantly reduced zinc neurotoxicity as well as zinc-induced AMPK activation, indicating the possible role of LKB1 as an upstream kinase for AMPK. In addition, we found that mRNA and protein level of Bcl-2 homology domain 3 (BH3)-only protein Bim, a pro-apoptotic Bcl-2 family member, was noticeably increased in zinc neurotoxicity in an AMPK-dependent manner. Consistently, caspase-3 activation in zinc neurotoxicity was also mediated by LKB1 and AMPK activation. These results suggest the possibility that AMPK is a key signaling molecule to induce zinc-induced neuronal death via up-regulation of Bim and resultant activation of caspase-3 in zinc neurotoxicity. **Keywords**: AMPK, brain ischemia, LKB1, Bim, caspase-3, neuronal death, zinc

Disclosures: J. Eom: None. **Y. Kim:** None.

Poster

591. Cell Death Mechanisms: Apoptosis and Mitochondria

Location: Hall A

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Topic: C.11. Neurotoxicity, Inflammation, and Neuroprotection

Support: CONACYT-128392

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Fundación Beltran-Morado para el Avance y Difusión de la Neurociencia en Veracruz

Title: Modulation of mitochondrial dynamics by high-extracellular glucose in nerve growth factor (NGF)-differentiated PC12 cells

Authors: *A. E. SOSA ESCALANTE[1], R. DIAZ-ESCARCEGA[1], J. MANZO-DENES[2], C. MORGADO-VALLE[2], L. BELTRAN-PARRAZAL[2];
[1]Doctorado en Investigaciones Cerebrales, [2]Ctr. de Investigaciones Cerebrales, Univ. Veracruzana, Xalapa, Mexico

Abstract: In the nervous system, high-extracellular glucose has been proposed as a cause of mitochondrial dysfunction, generating drastic changes in the mitochondrial dynamics, and

therefore damaging neurons. It is unknown whether high extracellular glucose affects directly the mitochondrial dynamics, or if it produces changes on other molecular mechanisms that affect indirectly the mitochondria. In the presence of high-extracellular glucose, there are changes in the rates of mitochondrial fusion and fission (Kumari et al, 2012). However, there is not information regarding the effect of high-extracellular glucose on mitochondria number and length, and how could this affect fusion and fission rates. Here, we used PC12 cells differentiated to sympathetic-like neurons by NGF as a model of peripheral axons to measure mitochondrial velocity in the presence of high-extracellular glucose. We tested a high-extracellular glucose concentration (75 mM) and compared with control concentration (25 mM). After incubation period, we dyed mitochondria with the specific marker MitoTracker Green. Using fluorescence microscopy, we acquired time-lapse videos and generated kymographs of mitochondria. Our data shows that high-extracellular glucose decreases significantly the mitochondrial velocity from 0.233 ± 0.074 μm/s in control conditions to 0.012 ± 0.012 μm/s in 75 mM glucose. We did not found significant differences in the total number of mitochondria in both conditions, however we found a significant decrease in the number of short mitochondria. Our results suggest the 75 mM extracellular glucose modulates mitochondrial transport and decreases mitochondrial velocity in PC12 cells differentiated to neurons.

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Poster

591. Cell Death Mechanisms: Apoptosis and Mitochondria

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Swedish Research Council (K2012-99X-21988-01-3)

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Title: The effect of dichloroacetate on mitochondrial metabolism and brain injury after hypoxia ischemia in neonatal mice

Authors: ***T. LI**[1,2,3], Y. SUN[2,4], C. XIE[4,5], Y. ZHANG[4,3], K. ZHOU[4,5], K. BLOMGREN[4,5], C. ZHU[2,4];

[1]Gothenburg Univ., Gothenburg, Sweden; [2]Dept. of Pediatrics, Third Affiliated Hosp. of Zhengzhou Univ., Zhengzhou, China; [3]Zhengzhou Children's Hosp., Zhengzhou, China; [4]Ctr. for Brain Repair and Rehabil., Inst. of Neurosci. and Physiology, Univ. of Gothenburg, Gothenburg, Sweden; [5]Dept. of Women's and Children's Hlth., Karolinska Univ. Hosp., Stockholm, Sweden

Abstract: Background: Dichloroacetate (DCA) is a small molecule that crosses the blood-brain barrier and activates pyruvate dehydrogenase (PDH). DCA shows substantial efficacy in a variety of brain injury models, but there is no report yet on its efficacy in neonatal brain injury. **Objective:** To evaluate the therapeutic effectiveness of DCA treatment in neonatal mice after hypoxia-ischemia (HI). **Design/Methods:** Nine-day-old male mouse pups were subjected to unilateral HI, and 100 mg/kg DCA was injected intraperitoneally immediately after HI. Additional DCA injections were administered 24 h and 48 h after HI, and the extent of brain injury was evaluated 72 h after HI. Some pups were sacrificed 24 h after HI and the mitochondrial fraction was isolated. **Results:** Brain injury, as indicated by infarction volume, was reduced by 54.2% from 10.80 mm^3 ± 1.86 mm^3 in the vehicle-only control group to 4.94 mm^3 ± 1.05 mm^3 in the DCA-treated group 72 h after HI (p=0.008). Injury was reduced in the cortex, hippocampus, thalamus, and striatum, and the protective effect was greatest in the cortex and thalamus. Furthermore, treatment with DCA significantly reduced white matter loss analyzed by measuring the MBP-positive volume (p=0.018). Caspase-3 activity was increased dramatically 24 h after HI, and DCA treatment reduced caspase-3 activation significantly (p=0.0421). PDH activity in the mitochondria was decreased in the ipsilateral hemisphere after HI compared with the contralateral hemisphere (p=0.0037), and DCA treatment prevented the decrease in PDH activity. The amount of acetyl-CoA in mitochondria was significantly higher after HI with DCA than that of with PBS treatment (p=0.024). **Conclusion**: DCA treatment in neonatal mice reduced HI brain injury. This effect might be related to the activation of PDH and a subsequent reduction in lactate acidosis, caspase-3 activation and neuronal cell death.

Disclosures: T. Li: None. **Y. Sun:** None. **C. Xie:** None. **Y. Zhang:** None. **K. Zhou:** None. **K. Blomgren:** None. **C. Zhu:** None.

Poster

592. Neuro-Oncology I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 592.01/H36

Topic: C.12. Neuro-Oncology

Support: Penn State College of Medicine Department of Neurosurgery Departmental Support grant

Penn State College of Medicine Department of Pharmacology Departmental Support grant

Penn State College of Medicine Junior Faculty Development grant

Title: Gene expression profile in glioblastoma multiforme

Authors: *N. CARKACI-SALLI[1], J. M. SHEEHAN[2], J. W. BACCON[3], T. ABRAHAM[4], K. E. VRANA[1], R. E. HARBAUGH[2], M. GLANTZ[2];
[1]Dept. of Pharmacol., [2]Dept. of Neurosurg., [3]Dept. of Pathology, [4]Imaging Core Facility, Penn State Col. of Med., Hershey, PA

Abstract: The most aggressive type of brain tumor is glioblastoma multiforme (GBM). Currently, temozolomide (TMZ), combined with radiation, is the most effective therapy for GBM, but chemoresistance, that occurs in tumors, limits the efficacy of this treatment. To understand the molecular and cellular processes that underlie temozolomide resistance in GBM tumors we investigated alterations in protein expression, gene expression in primary GBM tumors from patients with different survival phenotypes (primary tumors for which there was not tumor recurrence after TMZ treatment) and patient primary tumors for which there was tumor recurrence. After proteomics analysis 92 spots out of over 2200 protein spots were found to be differentially-expressed. Of these, 16 up-regulated proteins and 15 down-regulated spots were chosen for identification by mass spectrometry. Individual specimens subjected to gene expression analysis Gene expression of Vimentin (VIMA) (P=0.01)(1.8 fold decreased in proteomics), LIM and SH3 domain protein (LASP1) (P=0.01) (1.9 fold decreased in proteomics), AnnexinA2 (ANXA2) (p=0.01) (3.2 fold decreased in proteomics) and AnnexinA5 (ANXA5)(P=0.01) (4.4 fold increased in proteomics), Coactosin-like protein (COTL1) (0.05) (3.5 fold increased in proteomics) , S100 calcium binding protein A9 (S10A9)(P=0.04) (3.7 fold increased in recurrent patients' primary tumor in proteomic) were found significantly different. Multidrug resistance gene (MDR1) (P=0.02), UDP-glucose ceramide glucosyltransferase (UGCG) (p=0.02), C-X-C chemokine receptor type 4 (CXCR4)(P=0.04) gene expression elevated in the recurrent tumor specimens in the targeted genes. These results suggest that VIMA, LASP1, AnnexinA2, AnnexinA5, COTL1, S10A9, MDR1, UGCG and CXCR4 were significantly plays role on recurrence of GBM tumors.

Disclosures: N. Carkaci-Salli: None. **J.M. Sheehan:** None. **J.W. Baccon:** None. **T. Abraham:** None. **K.E. Vrana:** None. **R.E. Harbaugh:** None. **M. Glantz:** None.

Poster

592. Neuro-Oncology I

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Topic: C.12. Neuro-Oncology

Support: NIH T32 NS047987

ENDURES Grant from the James S. McDonell Foundation

NIH T32 GM008152

Title: Cortical thickness in the contralesional hemisphere is related to survival length and tumor diffusivity in long-term survivors of glioblastoma multiforme

Authors: *C. DE LOS ANGELES, K. I. ALPERT, J. JACOBS, A. W. RADEMAKER, J. J. RAIZER, K. R. SWANSON, L. WANG;
Northwestern U Feinberg Sch. of Med., Chicago, IL

Abstract: Background: Patients with glioblastoma multiforme (GBM) provide a clinical population to study brain structural response to a lesion. GBM patients survive a median of 16 months with a small subset living longer than three years (reported rates: 3-10%). Some information exists about patient and tumor factors that relate to increased survival including younger age, higher Karnofsky Performance Status score, and certain tumoral gene mutations. Our study was concerned with identifying a neuroimaging marker of long-term survival using the presenting diagnostic magnetic resonance imaging (MRI) scan. This study assessed structural neural compensation by examining the contralesional (opposite hemisphere of tumor) hemisphere cortical thickness in GBM patients. Methods: We computed contralesional gray matter cortical thickness using the pre-treatment, diagnostic T1-weighted MRI. Cortical thickness was determined using Freesurfer. These structural measures were categorized as less than or greater than the population median. Days of survival was calculated from date of diagnosis until death. $\chi 2$ and logistic regression analyses were performed in SPSS. Patients who lived longer than three years were considered long term survivors. Results: In our preliminary studies, we found that in right-sided temporal lobe GBM patients (n = 39), cortical thicknesses within regions of the contralesional temporal lobe were associated with or showed a trend toward significance with long-term survival after controlling for age at diagnosis, sex, and tumor volume (entorhinal cortex $p = 0.040$; transverse temporal cortex $p = 0.074$). Moreover, cortical thicknesses in a region that was thicker in long-term survivors, the tranverse temporal cortex, positively correlated to patient tumor-specific diffusivity measures ($r = 0.626$, $p = 0.001$); more diffuse tumors displayed greater contralesional cortical thickness. Conclusions: In long-term survivors with GBM, increased contralesional cortical thickness is seen at diagnosis and related to tumor diffusivity, suggesting brain structural compensation. Work is ongoing to assess other

regions and to further understand the relationship between contralesional brain structural measures, tumor characteristics, and survival.

Disclosures: **C. De Los Angeles:** None. **K.I. Alpert:** None. **J. Jacobs:** None. **A.W. Rademaker:** None. **J.J. Raizer:** None. **K.R. Swanson:** None. **L. Wang:** None.

Poster

592. Neuro-Oncology I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 592.03/H38

Topic: C.12. Neuro-Oncology

Title: RNA-seq expression profiling of ion channels in glioblastoma stem cells

Authors: *J. POLLAK[1], P. J. PADDISON[2], R. C. ROSTOMILY[3,4], J.-M. RAMIREZ[1,3]; [1]Seattle Children's Res. Inst., Seattle, WA; [2]Human Biol. Div., Fred Hutchinson Cancer Res. Ctr., Seattle, WA; [3]Dept. of Neurosurg., [4]Inst. for Stem Cell and Regenerative Med., Univ. of Washington, Sch. of Med., Seattle, WA

Abstract: Glioblastoma multiforme (GBM) is a prevalent and highly aggressive type of brain tumor. Glioblastoma stem cells (GSCs) play a major role in tumor formation and malignancy owing to their rapid self-renewal, invasiveness, and chemotherapeutic resistance. Evidence suggests that disruption of ion balance through ion channel and transporter perturbation within glioma cells contributes to malignant invasion and proliferation. Neural activity from surrounding brain regions may also augment glioma malignancy, suggesting a role for voltage- or ligand-dependent communication between glioma cells and surrounding neurons. To comprehensively assess the expression of multiple families of ion channels, transporters, and receptors that may contribute to glioma malignancy, we profiled the transcriptomes of patient-derived GSCs using RNA-seq analysis. Nineteen distinct lines of GSCs, which were derived from patient GBM tumors and propagated as stem cell cultures, were processed in triplicate for RNA sequencing. GSC samples were processed and analyzed in tandem with transcriptome data from human astrocyte and neural stem cell lines. Unique subsets of ion channels, transporters, and neurotransmitter receptors were identified by Gene Set Enrichment Analysis (Broad Institute) to be highly enriched across multiple lines of GSCs compared with astrocytes and neural stem cell controls. These results were compared with transcriptome analysis of bulk GBM tumor cells and normal brain tissue from The Cancer Genome Atlas in order to identify ion channels unique to GSCs. Based on their ion channel expression profile alone, GSC lines clustered without bias by GBM molecular subtype classification, and expression levels of

individual ion channels significantly correlated with molecular subtype. Real-time PCR analysis confirmed expression of genes of interest across multiple GSC lines. These data suggest that candidate ion channels and transporters may be unique identifiers of glioblastoma stem cells compared with other neural and tumor cell types and may play an important role in GSC malignant properties; the functional implications of these findings will be discussed.

Disclosures: J. Pollak: None. **P.J. Paddison:** None. **R.C. Rostomily:** None. **J. Ramirez:** None.

Poster

592. Neuro-Oncology I

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Program#/Poster#: 592.04/H39

Topic: C.12. Neuro-Oncology

Support: NPRP 6 - 089 - 3 - 021

Title: Cisplatin (CDDP) modifies the protein expression of IP3R and RYR as well as interacts with Ca^{2+} -ATP-ase dependent calcium management of SH-SY5Y neuroblastoma cells

Authors: *D. BUSSELBERG[1], A. SAYED[2], E. VARGHESE[2], A.-M. FLOREA[3]; [1]Weill Cornell Med. Col. In Qatar, Doha, Qatar; [2]WCMC-Q, Doha, Qatar; [3]Neuropathology, Univ. Dusseldorf, Dusseldorf, Germany

Abstract: Neuroblastoma is a childhood cancer with limited treatment options. While chemotherapy with cisplatin (CDDP) is used in current treatment schemes the underlying mechanisms behind successful anticancer treatment are yet not well understood. It is now accepted that CDDP modulates the intracellular calcium signal ($[Ca^{2+}]_i$) due to a facilitation of calcium entry from the extracellular space. Therefore, here we investigate whether CDDP treatment of neuroblastoma cells will result in changes of the protein expression of IP3R and RYR (ITPR1, ITPR3, RYR1, and RYR3) and whether the Ca^{2+} -ATP-ase dependent calcium management is changed after the application of CDDP. Confocal microscopy imaging of ITPR1, ITPR3, RYR1, and RYR3 show that only RYR1 has a nuclear localization however, due to CDDP treatment (2.5 or 5μM CDDP for 24h) it was found translocated into the cytoplasm of neuroblastoma cells. In the same experimental conditions, the FACS analysis of SH-SY5Y cells showed no significant changes in expression of RYR1, RYR3 and ITPR1, but was an increase in ITPR3 (from 32% to ~50%). To further explore the role of CDDP in Ca^{2+} release from SH-SY5Y, cells labeled with Fura2-AM were treated with CDDP (5μM) in calcium free media.

When CDDP was applied to neuroblastoma cells, after pre-treatment with thapsigargin, the time till the rise of calcium was observed increased by 7-9 times, and by 6-times when added before and after treatment with thapsigargin. The slope (time to reach the calcium peak) was doubled. Recovery was prolonged in a similar way. Overall, CDDP changes the expression and localization of IP3R and RYR and modulates the Ca^{2+} -ATP-ase dependent calcium management of neuroblastoma cells.

Disclosures: D. Busselberg: None. **A. Sayed:** None. **E. Varghese:** None. **A. Florea:** None.

Poster

592. Neuro-Oncology I

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Program#/Poster#: 592.05/H40

Topic: C.12. Neuro-Oncology

Support: R01NS078223

Title: Alterations in functional connectivity due to brain tumor growth in a mouse model of glioma

Authors: *I. ORUKARI[1], A. Q. BAUER[2], E. A. SLAT[3], J. B. RUBIN[3], J. P. CULVER[2]; [1]Radiology, Washington Univ. In St Louis, St Louis, MO; [2]Radiology, [3]Pediatrics, Washington Univ. in St Louis, St Louis, MO

Abstract: Background: Gliomas are known to cause significant neuropsychological deficits in humans. We assessed the effects of tumor growth on resting-state functional connectivity in a mouse model of glioma. The resting-state functional connectivity data was obtained using functional connectivity optical intrinsic signal (fcOIS). This technique allowed us to perform functional neuroimaging on the small mouse brain. Methods: Gliomas cells (10^5 U87) were stereotactically injected into the cortical region in between the motor cortex and hindpaw and forepaw somatosensory cortex of adult nude mice. A plastic cover slip was affixed to the exposed skull of the mice for serial OIS imaging. OIS imaging was performed following our previously published protocol [1]. Seed based functional connectivity analysis was performed on the OIS images to monitor how brain tumor growth affects functional brain networks. Bilateral functional connectivity maps - maps of the correlation value between a pixel and the corresponding pixel in the contralateral hemisphere - were obtained as a metric of functional network disruption. Results: The region of decreased bilateral functional connectivity increased in size with time (Figure 1). Conclusions: We have shown that fcOIS is capable of detecting

alterations to brain function due to brain tumor growth. Our data show that tumor tissue becomes functionally disconnected from the contralateral hemisphere. Ongoing studies are incorporating bioluminescence to independently track the number of tumor cells to provide an improved estimate of the tumor size. A better understanding of the role brain tumors play in the development of functional brain deficits may lead to improved outcomes after neurorehabilitation. Citation: 1.White BR, Bauer AQ, Snyder AZ, et al. (2011) Imaging of functional connectivity in the mouse brain. PLoS ONE 6(1)

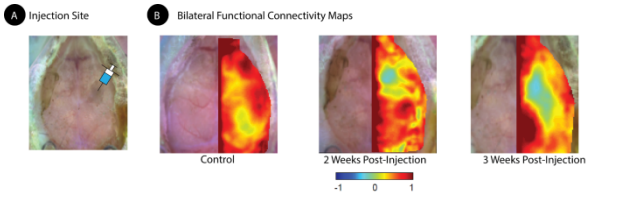

Fig. 1 Functional connectivity measures during tumor growth. (a) image of the mouse skull showing bregma and lambda sutures, and the injection sited (b) homotopic contralateral functional connectivity for time points before injection (control) and 2 weeks and 3 weeks after injection.

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Poster

592. Neuro-Oncology I

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College of Medicine

Field Neurosciences Institute

John G. Kulhavi Professorship

CMU Summer Scholar Research Grant

Title: Treating glioblastoma multiforme with bone marrow-derived mesenchymal stem cells

Authors: *L. D. HUFFMAN[1,2], K. R. IDYLE[1,2], A. CRANE[1,2], A. K. ANTCLIFF[1,2], D. J. DUES[1,2], K. D. FINK[1,2], J. ROSSIGNOL[1,2,3], G. L. DUNBAR[1,2,4,5];
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[4]Dept. of Psychology, Central Michigan Univ., Mount Pleasant, MI; [5]Field Neurosciences Inst., Saginaw, MI

Abstract: Glioblastoma multiforme (GBM) is one of the most aggressive and infiltrative primary tumor formations of the central nervous system. Current therapies are ineffective in eradicating this deadly type of tumor. In fact, the resurgence of GBM is almost inevitable and patient outcome following diagnosis remains dismal. Therefore, a novel and efficacious therapy is desperately needed to prevent tumor resurgence and improve patient outcome and quality of life. Mesenchymal stem cells (MSCs) have recently become a very popular avenue for the delivery of a variety of molecules and substances, and of particular interest to this project is their ability to release endogenous anti-inflammatory cytokines, such as interleukin-10 (IL-10). Importantly, solid tumors often secrete pro-inflammatory cytokines in an effort to increase angiogenesis and nutrient support to promote further proliferation. Specifically, the MSC therapy utilized in this study aimed to diminish this pro-inflammatory effect and ultimately slow and eradicate tumor progression. To these ends 24 rats were randomly placed into three groups: SHAM controls (n=8) received only vehicle treatments; the F98 group (n=8) received only a transplantation of F98 tumor cells; and the F98+MSC group (n=8) received a transplantation of MSCs seven days post-F98 transplantation. Stem cell grafts were placed adjacent to the tumor bed in order to promote the optimal release of anti-inflammatory signaling molecules. All animals were euthanized 21 days following F98 transplantations and histological analyses were performed to compare tumor size and inflammatory response between each group. Results indicated that the ipsilateral MSC treatment was unable to affect the inflammatory response produced by the tumor, nor significantly mitigate tumor growth. However, current studies aim to investigate the optimization of the stem cell graft to tumor cell ratio as well as the utilization of stem cells over-expressing these endogenous signaling molecules and their effects on tumor proliferation. Support for this study was provided by the Office of Research and Sponsored Programs at CMU, the College of Medicine, and the Field Neurosciences Institute and John G. Kulhavi Professorship.

Disclosures: **L.D. Huffman:** None. **K.R. Idyle:** None. **A. Crane:** None. **A.K. Antcliff:** None. **D.J. Dues:** None. **K.D. Fink:** None. **J. Rossignol:** None. **G.L. Dunbar:** None.

Poster

592. Neuro-Oncology I

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Support: NIH Grant AG026672

NIH Grant AG022550

NIH Grant AG027956

Title: Activation of a putative membrane androgen receptor increases the efficacy of the chemotherapeutic agent, temozolomide, in a human glioblastoma cell line

Authors: C. A. BROCK, A. BADEAUX MCGILVRAY, *M. SINGH;
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Abstract: Glioblastoma Multiforme (GBM) is a form of brain cancer with very poor prognosis such that the life expectancy of a person with this disease is about one year after diagnosis. Moreover, current treatment regimens are only able to extend the life span by mere months. Based on recent studies from our lab that identified a putative membrane androgen receptor (mAR), which when activated is capable of promoting cell death, we investigated whether exploitation of this receptor could increase the efficacy of current chemotherapeutic agents to combat this deadly and invariably lethal cancer. Using the human glioblastoma cell lines, A172 and T98G, our studies have shown that activation of the mAR (using testosterone or dihydrotestosterone conjugated to bovine serum albumin) not only sensitized the glioblastoma cells to temozolomide (TMZ), the current standard chemotherapeutic agent for GBM, but also suppressed the phosphorylation of Akt, a known survival-promoting factor. Further, in T98G cells that express high levels of O6-methylguanine DNA methyltransferase (MGMT), a DNA repair protein, activation of the mAR suppressed the expression of MGMT. Our data also suggest that these mechanisms may not be mutually exclusive such that inhibition of Akt phosphorylation in and of itself led to a reduction in MGMT expression. Collectively, our data support the targeting of a putative membrane androgen receptor as complementary treatment for glioblastoma.

Disclosures: C.A. Brock: None. **A. Badeaux McGilvray:** None. **M. Singh:** None.

Poster

592. Neuro-Oncology I

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Support: ONACyT #230537to AAS and CONCyT CB-169020 & SEP/CONCyT CB 134595

Title: Selective inhibition of survival of malignant astrocytoma by conjugated linoleic acid. Implication in anti-glioma therapy

Authors: A. S. SILVA-RAMIREZ[1], H. M. GONZALEZ-SANCHEZ[2], C. G. CASTILLO[2], A. ROCHA-URIBE[1], M. M. GONZALEZ-CHAVEZ[1], S. F. ALI[3], E. RANGEL-LOPEZ[4], A. SANTAMARIA[4], *C. GONZALEZ, V[1];
[1]Univ. Autonoma De San Luis Potosi, San Luis Potosi, Mexico; [2]Facultad de Medicina, Universiad Autonoma de San Luis Potosi, San Luis Potosi, Mexico; [3]Div. of Neurotoxicology, NCTR, Jefferson, AR; [4]Lab. de Aminoacids Excitadores, INNN, Mexico City, Mexico

Abstract: Glioblastoma multiforme (GBM), a fast-growing glioma that develops from astrocytes, is the most aggressive brain tumor in adults due to the rapid spread and failed treatments. Current chemotherapeutic agents are known to have a low therapeutic index in brain tumors, first due to the inability of anticancer agents to reach the brain tissue and secondly by their low selectivity towards cancer cells. Synthetic agonists of peroxisome proliferator-activated receptor-gamma (PPARγ) have shown decrease the viability of malignant astrocytoma cells without affecting the viability of primary astrocytes through a PPARγ independent pathway. Conjugated linoleic acid (CLA) is a natural PPARγ-agonist which cross blood-brain barrier and induce anti-tumor activity on glioblastoma cells; however, neither the mechanisms of action involved in the anti-glioma effect of CLA nor its toxicity on primary astrocytes has been elucidated. The aim of this study was to evaluate if CLA induced a selective cytotoxicity mediated by ROS or NO production on GBM without affecting primary astrocytes. Primary astrocytes isolated from male and female newborn Wistar rats and C6 glioma cells (rat GBM) were exposed for 24 or 72 hours to CLA (5, 10, 25, 50 and 100 uM) obtained by chemical synthesis assisted by microwave irradiation. Cell viability was measured by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cytotoxicity was determined by lactate dehydrogenase (LDH) test. The decrease in mitochondrial membrane potential (MMP) in apoptotic cells was associated with a reduction in the uptake of 3,3' dihexyloxacarbocyanine iodide (DiOC6(3)). Reactive oxygen species (ROS) were monitored using a 2',7'-dicholofluoroscein diacetate (DCFH-DA) assay and nitric oxide (NO) levels were determined using the Griess reaction. The PPARy involvement in cell signaling was assessed using the antagonist Bisfenol a diglicidil eter (BADGE). CLA treatments, since 24 hours, resulted in a significant decrease in cell viability of GBM without affecting primary astrocytes. The PPARy antagonist did not block the anti-glioma effect induced by CLA, indicating that the receptor is not involved in the mechanism of action. No significant changes in extracellular LDH or NO levels were detected. Data indicate that CLA exposure activates oxidative stress pathways, interferes with the mitochondrial electron transport chain and induces apoptosis, suggesting that CLA may represent a novel adjuvant therapeutic alternative in the treatment of GBM without causing adverse side effects. However, additional experiments are needed to determine the mechanism of action involved.

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Poster

592. Neuro-Oncology I

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Program#/Poster#: 592.09/H44

Topic: C.12. Neuro-Oncology

Support: Tubitak 113S083

Ataturk University BAP 2011270

Title: Effects of irinotecan nanoparticles on viability rates of glioblastoma multiforme and neurons

Authors: ***H. AHMET**[1], A. TAGHİZADEHGHALEHJOUG[2], U. OKKAY[2], N. TASPINAR[2], K. NALCI[2], M. TASPINAR[5], M. CETIN[3], A. UYANIK[4], S. BUTUNER[2];
[1]Ataturk Univ. Loj 48. Block No:7, [2]Dept. of Med. Pharmacol., [3]Dep. of Pharmaceut. Technol., [4]Dep. of Intrnl. Medicine- Nephrology, Ataturk Univ., Erzurum, Turkey; [5]Med. Biol., Yuzuncu Yil Univ., Van, Turkey

Abstract: Introduction: It is crucial to development of technology based, efficient tumor cell-targeted therapies for treating GBM. Polymeric nanoparticles (PNPs), especially poly-(DL-lactic-co-glycolic) acid (PLGA), have been used as an anti-tumor drug delivery vehicle which carries drug into the targeted tumor cells by their unique biodegradable properties, controlled release and intrinsic encapsulated empty area. Irinotecan, a semi-synthetic competitive analogue of topoisomerase-I enzyme, is an important and affective chemotherapeutic. It shows high activity against a wide spectrum of malignancies, including GBM. It has been reported that irinotecan loaded liposome useful for colorectal cancer (1). Matherial and method: For this study ethical permission is taken with the number 36643897-13. Brain cortex were obtained from 6 Sprague Dawley Rat which were one day old. U87MG culture were obtain from Van Yuzuncu Yil university. Cell cultures were performed. 100 Sprague Dawley Rats (250±10 gr) were chosen and performed GBM model using U87MG cell line. 8×105 cells were injected stereotactically into the brain; 1mm anterior to bregma, 2.5mm left to bregma and 4mm below into the nigrostriatal region. 15 days after injection drugs were injected directly into cancer region. From sections in pathology, the tumor areas were measured using cavalier principle. Results and

Discussion: Irinotecan was found effective on cancer cells. PLGA didn't give any damage alone. PLGA+irinotecan can be used for GBM therapy *in vivo*. PLGA didn't decrease the activity of irinotecan. Irinotecan + PLGA doses found more effective on cancer cells. We can postulate that slower releasing *in vivo* may be more effective on cancer cells. References: 1-Park, J., H. V. Pham, K. Mogensen, T. I. Solling, M. Vad Bennetzen and K. N. Houk (2015). "Hydrocarbon Binding by Proteins: Structures of Protein Binding Sites for >/=C Linear Alkanes or Long-Chain Alkyl and Alkenyl Groups." J Org Chem

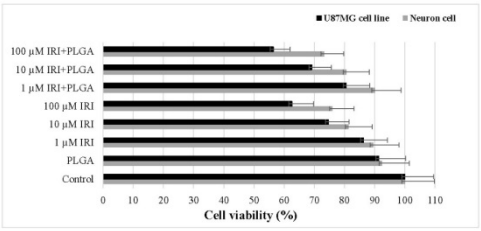

Table 1: Therapy of irinotecan with and without PLGA on neuronal and U87MG cancer cells.

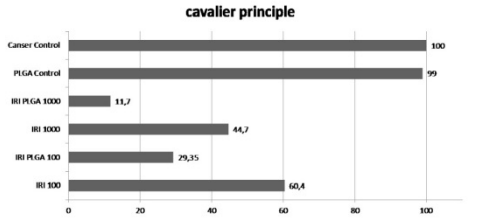

Table 2: Pathological evaluation for animal brain tissues with irinotecan/PLGA against control groups.

Disclosures: **H. Ahmet:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Tubitak 113S083, Ataturk University BAP 2011270. **A. TaghİzadehghalehjouG:** A. Employment/Salary (full or part-time):; Tubitak 113S083. **U. Okkay:** A. Employment/Salary (full or part-time):; Tubitak 113S083. **N. Taspinar:** A. Employment/Salary (full or part-time):; Tubitak 113S083. **K. Nalci:** A. Employment/Salary (full or part-time):; 113S083. **M. Taspinar:** None. **M. Cetin:** None. **A. Uyanik:** None. **S. Butuner:** A. Employment/Salary (full or part-time):; 113S083.

Poster

592. Neuro-Oncology I

Location: Hall A

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Topic: C.12. Neuro-Oncology

Support: California Institute for Regenerative Medicine (CIRM) TR3-05641

Title: Expression patterns of multiple antigens evaluated by immunochemistry in individual glioblastoma patient samples

Authors: *M. E. BARISH[1], L. WENG[2], Y. ZHAI[2], M. D'APUZZO[3], B. BADIE[4], S. J. FORMAN[5], C. E. BROWN[2];
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Abstract: Cellular heterogeneity is a hallmark characteristic of ostensibly similar cell populations occurring during neural and glial development, and during tumorigenesis and tumor progression. For the latter case, large collections of formalin-fixed paraffin embedded (FFPE) clinical specimens are a valuable resource for evaluating gene expression across large study cohorts. Many of these patient samples consist of serial tumor sections each stained for a single antigen by chromogenic immunohistochemistry (IHC), as is standard clinical pathology practice. Quantifying multiple tumor related antigens in the context of GBM tissue is an essential step towards understanding the fundamental biology of these tumors as well as developing novel targeted therapies. Towards this end, we have developed methods for combining semi-quantitative analysis of IHC processed tumor sections with regional annotation by a clinical pathologist. This has allowed us to consider patterns of antigen co-expression as well as spatial relationships with tumor structures and physiological status. We will present observations on expression of tumor-associated antigens IL13Rα2, HER2 and EGFR, and associations with proliferation as indicated by Ki67 expression and the vasculature as marked by the endothelial cell marker CD34.

Disclosures: **M.E. Barish:** None. **L. Weng:** None. **Y. Zhai:** None. **M. D'Apuzzo:** None. **B. Badie:** None. **S.J. Forman:** None. **C.E. Brown:** None.

Poster

592. Neuro-Oncology I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 592.11/H46

Topic: C.12. Neuro-Oncology

Support: Regione Autonoma della Sardegna, LR7/2007-CRP10810/2012

Title: Enhancement of human neuroblastoma cell apoptosis by combined treatment with valproic acid and interferon-β

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Abstract: Type I interferons (IFNs), including IFN-α and IFN-β, possess antitumoral activity and have been proposed to be potentially useful in the treatment of neuroblastoma. We have previously shown that IFN-β causes cell death of human SH-SY5Y neuroblastoma cells by inducing apoptosis through the intrinsic mitochondrial pathway (Dedoni et al. J. Neurochem. 115,1421-1433, 2010). As valproic acid, an histone deacetylase inhibitor (HDACi) has been reported to enhance the antitumoral effects of type I IFNs, in the present study we have examined the effects of this drug on IFN-β-induced apoptosis of neuroblastoma cells. We found that prolonged exposure (24 h) of SH-SY5Y cells to therapeutic concentrations of valproic acid (0.6-1 mM) had no effect on cell viability. However, when combined with IFN-β, valproic acid markedly enhanced cell apoptosis induced by the cytokine, as demonstrated by the increase in annexin V staining, caspase activation and poly-(ADP ribose) polymerase (PARP) cleavage. Acetylation of histone 2B at Lys5 was markedly enhanced by valproic acid, but this response was not affected by co-treatment with IFN-β. Conversely, valproic acid enhanced the IFN-β-stimulated Tyr-phosphorylation of STAT1, which is crucial for cytokine-induced apoptosis. Sodium butyrate (1 mM), another HDACi, elicited similar potentiating effects on IFN-β-induced apoptosis and STAT1 phosphorylation, whereas valpromide (1 mM), which did not enhance histone acetylation, had no effects. MYCN-amplified human LAN-1 neuroblastoma cells displayed no sensitivity to the pro-apoptotic activity of IFN-β, but underwent apoptosis when treated with either valproic acid or sodium butyrate. Co-treatment of LAN-1 cells with IFN-β and HDACi, but not valpromide, resulted in a significant increase in cell apoptosis. These data show a synergistic interaction of IFN-β and valproic acid in promoting neuroblastoma cells apoptosis, which appears to be related to enhancement of histone acetylation.

Disclosures: S. Dedoni: None. **M.C. Olianas:** None. **P. Onali:** None.

Poster

592. Neuro-Oncology I

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Topic: C.12. Neuro-Oncology

Support: NIH Grant R01NS082851

Title: MMPs facilitate perivascular glioma cell invasion

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Abstract: Primary brain tumors, gliomas, have thus far evaded effective treatment making them a tremendous challenge clinically. This is due in part to the aggressive, invasive nature of glioma cells to infiltrate the surround brain away from the main tumor mass, making complete surgical resection impossible. Glioma cells primarily invade using pre-existing secondary structures such as white matter tracts or blood vessels. It has recently been shown that as glioma cells co-opt the vasculature, astrocytic endfeet are displaced leading to breakdown of the blood-brain barrier. Matrix metalloproteinases (MMPs), a large family of zinc-dependent endopeptidases, function in normal physiological settings to remodel the extracellular matrix (ECM). For example, they are critical in the wound healing process. MMPs have also been implicated in many disease states, of which gliomas are included. Glioma cells express MMPs-2, 3, & 9 and the ability of tumor cells to digest the ECM by secreting enzymes has been shown to correlate with their invasiveness. While MMPs have long been believed to contribute to the migration of glioma cells away from the main tumor mass, the role that MMPs play in perivascular glioma cell invasion, specifically whether MMPs mediate the cleavage of astrocytic endfeet anchoring proteins has yet to be explored. We hypothesized that perivascular gliomas release MMPs that digest basement membrane components responsible for anchoring astrocytic endfeet to the vascular surface. Using a clinically relevant mouse model of glioma and quantitative immunohistochemistry, we confirmed the expression of MMPs in and around glioma cells associated with the vasculature. In addition, we identified substrates for these released MMPs—components of the basement membrane and the endfoot anchoring complex. Using confocal time-lapse microscopy of acute slice glioma invasion preparations we were able to compare rates of perivascular glioma invasion with and without broad-spectrum MMP inhibitor batimastat (BB-94), to conclude that MMPs are essential for perivascular glioma invasion. Finally, we utilized a human glioma cell line that stably expresses a recombinant GPCR (RASSL), which activates Ca^{2+} signaling in response to a synthetic ligand, and genetically encoded Ca^{2+} sensor GCaMP3. This cell line used in conjunction with our acute slice glioma invasion preparation allowed for the determination that MMP release from perivascular glioma cells is a Ca^{2+} dependent process. Taken together, our data suggests that MMPs are essential for perivascular glioma cell invasion and help to mediate the displacement of astrocytic endfeet from the vascular surface.

Disclosures: **E.G. Thompson:** None. **H.W. Sontheimer:** None.

Poster

592. Neuro-Oncology I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 592.13/H48

Topic: C.12. Neuro-Oncology

Title: Modeling high-grade glioma via directed genome instability

Authors: ***C. V. CAMACHO**[1], T. SHAW[2], C. QU[2], G. WU[2], Y. FAN[2], Y. LI[2], S. M. DOWNING[1], H. R. RUSSELL[1], S. CHANG[5], J. ZHANG[2], S. J. BAKER[3], D. W. ELLISON[4], P. J. MCKINNON[1];
[1]Genet., [2]Computat. Biol., [3]Developmental Neurobio., [4]Pathology, St Jude Children's Res. Hosp., Memphis, TN; [5]Lab. Med., Yale Univ., New Haven, CT

Abstract: Accumulation of DNA lesions, due to defects in DNA repair mechanisms, can have a profound effect on development and induce mutagenic events that ultimately lead to cancer. We have developed mouse models targeting specific factors involved in DNA repair and telomere maintenance with which to assess the impact of genome instability towards tumorigenesis in the brain. DNA double-strand breaks (DSBs) are repaired by two distinct pathways, non-homologous end joining (NHEJ) or homologous recombination (HR). These pathways have been disabled in the mouse by brain region-specific deletions of DNA ligase IV (Lig4) or BRCA2, respectively. We also developed models in which normal regulation of topoisomerase-1 was compromised via inactivation of ATM or TDP1. Finally, telomere maintenance was disrupted by inactivation of Pot1a, a protein essential for proper telomere capping. Importantly, these factors are all known to underpin specific human cancers, including brain tumors. Loss of these factors during development has a cumulative effect on genome stability, resulting in a high frequency of tumor formation. These tumors were high-grade gliomas (HGG) and showed oligodendroglial and/or astrocytic morphology or mixed glial and primitive neuroectodermal tumor-like phenotypes. To understand the molecular basis of these tumors, we undertook RNA and exome sequencing. Sequencing of the transcriptome revealed alterations in gene expression that resulted in a heterogeneous set of HGG. Gliomas exhibited molecular signatures of all subtypes of the disease, suggesting transformation can occur in various cells of origin. Importantly, we identified both novel and previously described gene fusions and translocations involving potent oncogenes such as Met, Pdgfrα, Alk, and B-Raf. Exome sequencing also revealed tumor-specific somatic mutations in chromatin remodeling factors and the serine/threonine kinase B-Raf. Significantly,

the mutation observed in B-Raf corresponds to the V600E mutation observed in many human cancers, including some primary nervous system tumors. These new models will provide important tools to uncover the key genetic events that drive gliomagenesis in the context of neural development.

Disclosures: **C.V. Camacho:** None. **T. Shaw:** None. **C. Qu:** None. **G. Wu:** None. **Y. Fan:** None. **Y. Li:** None. **S.M. Downing:** None. **H.R. Russell:** None. **S. Chang:** None. **J. Zhang:** None. **S.J. Baker:** None. **D.W. Ellison:** None. **P.J. McKinnon:** None.

Poster

592. Neuro-Oncology I

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Program#/Poster#: 592.14/I1

Topic: C.12. Neuro-Oncology

Support: QNRF/NPRP 6-089-3-021

Title: The effect of pharmacological modulation of calcium signaling on the viability of human neuroblastoma cells

Authors: ***A. M. FLOREA**[1], G. REIFENBERGER[1], D. BÜSSELBERG[2];
[1]Heinrich Heine Univ. Düsseldorf, Uniklinikum, Düsseldorf, Germany; [2]Weill Cornell Med. Col. in Qatar, Doha, Qatar

Abstract: Neuroblastoma is a childhood cancer that urgently needs improved treatment schemes especially for the high-risk forms of the disease. Current treatment strategies include application of platinum complexes (CDDP, carboplatin), DNA alkylating agents and topoisomerase I inhibitors (e.g. TOPO). In this study we tested whether an array of calcium signaling modulators that target specific sites involved in calcium signaling are able to modify cell viability of SH-SY5Y, IMR32 and NLF human neuroblastoma cells. We tested the effect of (1) SERCA ATP-ase inhibitors: Thapsigargin (THAPS), Cyclopiazonic acid (CPZ); (2) IP3R inhibitor 2APB; (3) L-type calcium channel inhibitors verapamil (VERA) and nifedipine (NIFE); (4) mitochondrial transition pore inhibitor and calcineurin inhibitor Cyclosporine A (CYCLA); (5) RyR modulators Dantrolene (DANTR) and Ryanodine (RYA). The results show that in SH-SY5Y cells THAPS (0.02-2μM) was able to significantly reduce cell viability in a time and concentration dependent manner; highest cytotoxicity was observed after 72h time of exposure. Cyclopiazonic acid (0.2-20μM) was also cytotoxic in SH-SY5Y cells in a time and concentration dependent manner, but at a concentration 100-fold higher than THAPS. The IP3R inhibitor 2APB (2-100μM) was

cytotoxic in SH-SY5Y cells in a time and concentration dependent manner, but only the highest concentrations were cytotoxic after 72h of exposure. Cyclosporine A was also an effective cytotoxic drug in SH-SY5Y cells, with concentrations of 0.2-20μM showing reduced cell survival in a time and concentration dependent manner. The other modulators such as VERA (0.2-20μM), NIFE (0.2-20μM), DANTR (0.2-20μM), RYR (0.02-2μM), did not show cytotoxicity at the concentrations tested. When we compared the cytotoxicity of these inhibitors for the 72h time of exposure in SH-SY5Y, IMR32, NLF human neuroblastoma cells, we observed differential effect in regard to the cytotoxicity. For instance, THAPS (0.02-2μM) had highest cytotoxicity in NLF cells (20% cell survival), while THAPS cytotoxicity in IMR32 cells was between 80 % (0.2μM) to 60% (2μM) cell survival, and in SH-SY5Y 80% cell survival. CPZ was cytotoxic at the highest concentration tested (20μM) in SH-SY5Y and NLF cells but not in IMR32. Furthermore, the 100μM 2APB as well as CYCLA were cytotoxic in all three neuroblastoma cell lines tested. Overall, our *in vitro* data indicate that SERCA ATP-ase inhibitors as well as IP3R antagonists and mitochondrial/calcineurin modulators demonstrate cytotoxic activity against neuroblastoma cells.

Disclosures: **A.M. Florea:** None. **G. Reifenberger:** None. **D. Büsselberg:** None.

Poster

592. Neuro-Oncology I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 592.15/I2

Topic: C.12. Neuro-Oncology

Title: Insights into HuR multimerization in glioma

Authors: ***N. FILIPPOVA**[1], X. YANG[1], A. SOROCHINSKY[2], Z. GENTRY[3], L. B. NABORS[1];
[1]Neurol., Univ. of Alabama At Birmingham (UAB), Birmingham, AL; [2]VHHS, Birmingham, AL; [3]Vanderbilt Univ., Nashville, TN

Abstract: HuR is the mRNA binding protein (ELAV family) which is overexpressed in different types of cancer cells, including brain tumors. HuR overexpression and strong cytoplasmic localization in tumor tissue are associated with an aggressive tumor phenotype, chemoresistance, and pure patient outcomes. In our current report, we performed a comparison of HuR nuclear/cytoplasmic localization in an array of brain tumor samples (grades i-iv) and control brain tissue. We confirmed a mostly nuclear HuR localization in control brain tissue compared to HuR nuclear/cytoplasmic localization in brain tumors samples with an increase of HuR

cytoplasmic localization and intensity with increasing tumor grade. The analysis of HuR protein in the non-denatured condition Western blot revealed strong HuR protein multimerization in the cytoplasmic fraction of tumor samples. We found that HuR multimerization is stable in the presence of RNase treatment and could be partially decreased by the reducing condition. HuR protein multimerization in the cytoplasmic fraction was observed also in samples of patient derived xenolines (PDGx) and established glioma cell lines. We developed several assays including split Firefly Luciferase assay (N and C terminals parts of Firefly luciferase were attached to the C terminal end of HuR constructs), bioluminescence energy transfer (BRET) assay (between HuR-Renilla Luciferase and EGFP-HuR or HuR-EGFP constructs) to analyze HuR multimerization in U251 cells and to map HuR domains which come in close proximity during multimerization. In split Firefly Luciferase assay we were able to detect the luminescence signal from full length HuR constructs, HuR constructs truncated at 198 residue (before hinge region) and HuR constructs truncated at 244 residue (after hinge region), suggesting that the C-terminal edge of RM2, hinge region, and the C terminal edge of RM3 may come in close proximity as homo-oligomers during HuR multimerization and could affect the HuR multimerization conformation. This data was confirmed in BRET assay between HuR-Renilla Luciferase and HuR-EGFP constructs. The disruption of the HuR multimerization process in cell-based assays by targeting HuR protein redox state, or the hinge region function or RM3 domain were associated with a decrease of tumor cell proliferation and enhanced sensitivity to chemotherapeutic treatment. In summary, we provide evidence of HuR multimerization in cancer cells and propose possible pharmaceutical pathways for specific inhibition of HuR multimerization for cancer cells based on differentiation of targeted domains involved in multimerization.

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Poster

592. Neuro-Oncology I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 592.16/I3

Topic: C.12. Neuro-Oncology

Title: Morphological effects of curcumin on A172 cell line of human astrocytoma

Authors: ***M. B. GARRIDO ARMAS**[1,2], M. SALAZAR-GARCIA[3], S. OROZCO-SUAREZ[5], F. ARENAS-HUERTERO[4];

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Abstract: Morphological effects of curcumin on a172 cell line of human astrocytoma Cell death is a crucial physiological process that controls many vital functions, including development, morphogenesis, tissue homeostasis and defense against pathogens. Tumor cells can be sensitive or resistant to cell death. Many tumors initially respond to treatment with drugs and eventually develop multiple resistances due to the increase in drug injection mechanisms, or increase the capacity of DNA repair. These challenges have been stimulated interest in finding other cell death pathways that could be used to eliminating tumor cells, which have created the resistance phenotype. Various forms of cell death have been described, based on morphological criteria. Curcumin is a polyphenol compound extracted from *Curcuma longa* plant, which is commonly used in the preparation of oriental food, as well as mustard and curry. This kind of yellow spice has been used for thousands of years as traditional medicine in Asia, for the treatment of acne, psoriasis, dermatitis, among others. It is a molecule with pleiotropic effects and suppresses the transformation targets, proliferation and metastasis of malignant tumors. We found in our laboratory that Curcumin at 100 μM induces cell death and specific morphological characteristics on human astrocytoma cell line A172. Results show increase in size, presence of translucent accumulated vesicles in the cytoplasm, some with fusion, which produces the cytoplasmic membrane rupture. The vacuolization response started at 14 minutes of curcumin exposure, the cells were evaluated 1, 3 and 6 hours and at these times the response was reversible. There is no evidence of nuclear fragmentation, that's why apoptosis and necrosis were discarded. To evaluate autophagy cell death, the cells were analyzed with LysoTracker green and this labeling didn't localize into big vesicles inside the cells. At 24 hours of treatment, the changes were irreversible and the cells dead at 85%. It seems methuosis-like response. This cell response comes from the Greek "methuo" which means "drinking to intoxicate". It is distinct from other non apoptotic deaths since it involves macropinocytosis combined with defects in traffic independent of clathrin endocytic vesicles, which results in the presence of large vesicles which alter the integrity of the cell membrane. This response is reported by other authors, with other natural compounds like chalcons.

Disclosures: M.B. Garrido armas: None. **M. Salazar-garcia:** None. **S. Orozco-suarez:** None. **F. Arenas-Huertero:** None.

Poster

592. Neuro-Oncology I

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Topic: C.12. Neuro-Oncology

Support: FIUCOM Dept of Neuroscience start-up research grant

Title: Soluble adenylyl cyclase(sAC) modulates cell proliferation and survival in glioblastoma

Authors: *L. MICCI[1], C. CARDENAS[2], R. G. CORREDOR[3];
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Abstract: It is known that the second messenger cyclic adenosine monophosphate (cAMP) participates in cell proliferation and growth in the mammalian brain; however it is not clear how cAMP participates in glioblastoma, the most frequent, deadly and aggressive primary tumor of the central nervous system. Recently, a novel source of intracellular cAMP, the sAC, was identified. sAC is present in cytoplasm, nucleus and mitochondria of neurons and glia in the central nervous system, but contrary to transmembrane adenylyl cyclase , sAC is not activated by G-protein-coupled receptors (GPCR) but by intracellular calcium and bicarbonate, suggesting that sAC may be a critical modulator of cell metabolism. Although sAC has been shown to be present in some cancers like melanoma and prostate cancer, its potential role in cancer pathogenesis is still unknown. We investigated expression and function of sAC in four glioma-glioblastoma cell lines (H4, A172, U118 and U87) and found that western blot using two different anti-sAC antibodies targeting the sAC catalytic domain detects the protein at the molecular weight expected for the truncated form of sAC, but in addition, there is a characteristic unique band pattern identifiable for each cell line. Light microscopy allowed also for identification of characteristic cell behavior of cell lines in culture after sAC pharmacological inhibition with KH7. Cell quantification of the same cultures 5 hour and 24hour after sAC inhibition showed that sAC inhibition significantly impairs proliferation of glioblastoma cell lines in a dose-dependent manner where some cell lines are very sensitive to sAC inhibition compared to others. sAC-inhibition-mediated cell death was also observed with the most robust effect in H4 glioma cell line. These data suggest characteristic patterns of sAC expression for specific glioblastoma cell types and identifies a sAC-mediated cAMP signaling pathway as a potential target for diagnostic classification and treatment of glioblastoma.

Disclosures: L. Micci: None. **C. Cardenas:** None. **R.G. Corredor:** None.

Poster

592. Neuro-Oncology I

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Topic: C.12. Neuro-Oncology

Support: Conacyt Grant 127357

Title: Additive effects of the combined expression of tGAS1 and PTEN-LONG reducing the viability of glioma cells

Authors: *L. SANCHEZ[1], J. HERNANDEZ-SOTO[1], P. VERGARA[1], R. O. GONZALEZ[2], J. SEGOVIA-VILA[1];
[1]CENTRO DE INVESTIGACION Y DE ESTUDIOS AVANZADOS, Mexico City, Mexico;
[2]UNIVERSIDAD AUTONOMA METROPOLITANA, Mexico City, Mexico

Abstract: When GAS1 (Growth Arrest Specific 1) is expressed in glioma cells it induces cell arrest and apoptosis. We have previously demonstrated that the apoptotic process set off by Gas1 is caused by its capacity inhibiting the GDNF-mediated intracellular survival signaling. Furthermore, PTEN antagonizes the action of PI3K, but there are cancers in which PTEN is not active. Thus, it is important to investigate the potential additive effect of the overexpression of GAS1 and PTEN inhibiting tumor growth. We have already observed that GAS1 and PTEN have an additive effect inducing cell death. Moreover, it has also been shown that soluble forms of GAS1 and PTEN (tGAS1 and PTEN-LONG) are effective reducing tumor growth. Hence, we made a lentiviral vector with a 2A peptide-enabled dual expression system, which allows us to generate the two proteins from the control of a single promoter. The co-expression of tGAS1 and PTEN-LONG in U87 human glioblastoma cells induced a decrease in the activity of both ERK and AKT and reduced the number of viable cells expressing the transgenes. These outcomes were also observed in independent cell cultures in which conditioned medium containing tGAS1 and PTEN-LONG was administered. These data indicate that tGAS1 and PTEN-LONG act in both autocrine and paracrine manners. These effects were stronger than when each protein was individually expressed. All this together suggests that the combined treatment with tGAS1 and PTEN-LONG is a potentially interesting therapeutic approach for the treatment of gliomas.

Disclosures: L. Sanchez: None. **J. Hernandez-Soto:** None. **P. Vergara:** None. **R.O. Gonzalez:** None. **J. Segovia-Vila:** None.

Poster

592. Neuro-Oncology I

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Program#/Poster#: 592.19/I6

Topic: C.12. Neuro-Oncology

Title: Intratumoral modulation therapy for glioblastoma

Authors: M. COOPER[1], H. XU[2], C. DE OLIVEIRA[3], S. WHITEHEAD[3], S. SCHMID[3], *M. O. HEBB[2];
[1]Neurosci., [2]Clin. Neurolog. Sci., [3]Anat. and Cell Biol., Univ. of Western Ontario, London, ON, Canada

Abstract: **Background:** Glioblastoma (GBM) is the most common and malignant primary brain tumor in adults. Median survival with current therapies remains dismal at 12-18 months and there is a critical need for innovative and effective treatment strategies. The clinical indications for neuromodulation therapy in the brain are rapidly expanding and this technique is now the standard of surgical care for select neurological diseases (e.g., Parkinson's Disease). It is well known that glia-originated tumors are vulnerable to perturbations of the electrochemical environment; however, direct neuromodulation techniques have not been exploited for glioma management. **Methods:** Our group has developed an *in vitro* model to deliver continuous, low voltage electric current directly into GBM cultures, a technique we call intratumoral modulation therapy (IMT). GBM cell lines as well as primary GBM cells derived from operative specimens were studied for vulnerability to IMT without and with temozolomide (TMZ) chemotherapy or oncogene targeting strategies. **Results:** These studies demonstrated a marked vulnerability of patient GBM cells, but not primary neurons, to IMT with parameters that align with those clinically used for deep brain stimulation to treat various neurological diseases, or with externally applied devices to deliver alternating electric fields across the cranium of GBM patients. GBM cells treated with IMT undergo enhanced caspase 3-activated apoptosis, and develop markedly heightened sensitivity to TMZ. Uptake and biodistribution of siRNA was enhanced in primary GBM cells, along with target gene knockdown and functional effect, in the presence of IMT. **Conclusions:** These studies follow on the heels of reported significant advances using externally applied alternating electric fields in GBM patients. The proposed use of minimally invasive implantable stimulation devices offers distinct advantages, including direct lesion targeting for delivery of continuous IMT, titratible stimulation settings to maximize benefit and lessen off-target effects and low maintenance, concealed hardware for improved self-perception and quality of life. Results from these investigations will guide further studies to evaluate the *in vivo* efficacy of IMT for GBM.

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Poster

592. Neuro-Oncology I

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 592.20/I7

Topic: C.12. Neuro-Oncology

Title: Plexin-B2 signaling promotes tumorigenicity of glioblastoma stem-like cells through activation of STAT3

Authors: *Y. HUANG[1], R. TEJERO-VILLALBA[1], R. H. FRIEDEL[1,2], H. ZOU[1,2]; [1]Neuroscience, Icahn Sch. of Med. at Mount Sinai, New York, NY; [2]Neurosurgery, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Glioblastoma harbors a subpopulation of stem-like tumor propagating cells termed glioma stem cells (GSCs). The signaling pathways that promote malignant potency of GSCs remain to be identified. Here, we show that Plexin-B2, a semaphorin receptor, is highly expressed in patient-derived GSCs. Plexin-B2 deletion slowed down GSC growth and self-renewal *in vitro* and attenuated tumor formation *in vivo* in orthotopic transplantation assays. Plexin-B2 remains expressed in differentiated progenies of GSCs, and its ablation affects differentiation phenotypes. Furthermore, we identified a novel link between Plexin-B2 signaling and activation of the STAT3 transcription factor, a central regulator of glioma cell phenotypes. Our analysis of patient gene expression data revealed that Plexin-B2 upregulation in glioblastoma is correlated with high expression of STAT3. Plexin-B2 deletion in both GSCs and their differentiated progenies leads to marked reduction in STAT3 activation. Consistently, downstream targets of STAT3 were decreased in Plexin-B2 deficient GSCs and their differentiated progeny. Our preliminary data indicate that STAT3 activation is required for Plexin-B2 mediated function in GSCs and is mediated through activation of Rho GTPases. Together, our study elucidates a novel signaling cascade in glioma cells from membrane receptor Plexin-B2 to a nuclear transcriptional response mediated by STAT3.

Disclosures: Y. Huang: None. **R. Tejero-villalba:** None. **R.H. Friedel:** None. **H. Zou:** None.

Poster

592. Neuro-Oncology I

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Topic: C.12. Neuro-Oncology

Support: TTUHSC Seed Grant

Title: Targeted delivery of histone deacetylase inhibitor for anti-glioma therapy

Authors: L. ZOU, J. D. RODRIGUEZ, T. THOMAS, *H. DOU;
Dept. of Biomed. Sci., Texas Tech. Univ. Hlth. Sci. Ctr. (TTUHSC), El Paso, TX

Abstract: Introduction: The fundamental difficulties of anti-glioma therapy are across the BBB and specifically target to the tumor to enhance therapeutic efficacy and minimize side effect. Nanoparticles (NPs) containing mixed lipid monolayer shell and rabies virus glycoprotein (RVG) peptide as brain targeting ligand were developed for brain targeted delivery of entinostat, a histone deacetylase inhibitor, to treat malignant glioma. Materials and Methods: NPs were prepared and sized by extrusion through 100 nm membranes. Then, entinostat was loaded by transmembrane pH gradient method and RVG was conjugated by thiol-maleimide specific reaction. Entinostat loaded NPs conjugated with RVG (RVG-entinostat-NPs) were characterized by AFM, DLS and HPLC to measure the shape, surface morphology, particle size and the drug loading content. Fluorescent rDHPE and DiSC3(5) were used to label RVG-entinostat-NPs. MTT test was conducted to examine anti-glioma activities. Live image and histological sections were employed to detect RVG-entinostat-NPs *in vivo*. Results: RVG-entinostat-NPs were successfully prepared with the desirable size (139nm), narrow size distribution, spherical shape and high entinostat loading content. *In vitro* study showed that RVG-entinostat-NPs exhibited poor uptake by neurons and selective targeting to the brain tumor associated macrophages (TAMs) with controlled release. The toxicity to U87 was obtained by treatment of RVG-entinostat-NPs at concentrations of 10-2mM and above. *In vivo* studies revealed that RVG-entinostat-NPs were significant across the blood-brain barrier (BBB) and specific targeting to the brain. Histological analysis revealed that RVG-entinostat-NPs were obviously accumulated in brain of the mice. Importantly, live animal imaging and tumor growth evaluation showed that RV- entinostat-NPs significantly prevent glioma growth. Conclusions: We have been successfully developed RVG-entinostat-NPs to deliver entinostat for treatment of glioma. RVG-entinostat-NPs combine the superb trans-BBB capability and the TAMs targeting specificity providing an effective anti-gloma delivery system for further clinic use.

Disclosures: **L. Zou:** A. Employment/Salary (full or part-time):; Texas tech University Health Sciences Center at El Paso. **J.D. Rodriguez:** None. **T. Thomas:** A. Employment/Salary (full or part-time):; Texas tech University Health Sciences Center at El Paso. **H. Dou:** A. Employment/Salary (full or part-time):; Texas tech University Health Sciences Center at El Paso. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Texas tech University Health Sciences

Center. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Texas tech University Health Sciences Center.

Poster

592. Neuro-Oncology I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 592.22/I9

Topic: C.12. Neuro-Oncology

Support: VR-MH

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Vinnova

Title: Mechanism of transport and intracellular target of GlioStem: novel technology for near-immediate detection of glioblastoma-derived stem cell-like cells

Authors: A. GRACIAS[1], B. MIGLIORI[1], N. GIOTOPOULOU[1], E. KAVANAGH[2], M. BÄCK[3], P. NILSSON[3], B. JOSEPH[2], *O. HERMANSON[1];
[1]Dept. of Neuroscience, Karolinska Institutet, Stockholm, Sweden; [2]Dept. of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [3]Dept. of Chem., Linköping Univ., Linköping, Sweden

Abstract: Glioblastoma multiforme (GBM) is one of the most aggressive brain tumor types. Despite being one of the most well studied nervous system tumors, the median survival has not increased significantly and is 14.8 months with the best possible treatment including surgery, chemotherapy and radiation. One of the reasons for this poor prognosis is believed to be the existence of cancer stem cells. The GBM-derived stem cell-like cells (GSCs) have features of tumor-initiating cells (TICS) and can self-renew, leading to tumor formation. Previous studies from our lab have introduced a luminescent conjugated oligothiophene (LCO) named p-HTMI or GlioStem that specifically detects rat embryonic neural stem cells and GSCs, but not adult neural stem cells, differentiated cells of any kind, or other stem or cancer cells. By mere application to the cell culture dish, GlioStem labels in green more than 70% of the cells in populations of GSCs derived from three patients, within 10 minutes, a higher number when compared to CD133, a stem cell marker. The GlioStem-labeled cells overlapped with the more promiscuous marker CD271 (NGF receptor). The detection of human GSCs with GlioStem occurred without

triggering apoptosis or necrosis. GlioStem labeling was mostly cytoplasmic in embryonic neural stem cells as well as GSCs. Preliminary studies indicate an ER target of GlioStem. The side chain moiety is essential for its functionalization, and additional LCOs have been generated producing red fluorescence that currently is under verification for specificity and function. With regards to mechanism of uptake, our results indicated a passive uptake of GlioStem that required an intact cell membrane, verified using different permeabilization techniques. Its specificity, sensitivity, ease of use and detection by fluorescence microscopy and FACS suggests its potential clinical use in surgery. We are currently performing *in vivo* studies to verify GlioStem selectivity in GSCs when injected into NOD/SCID mice.

Disclosures: **A. Gracias:** None. **B. Migliori:** None. **N. Giotopoulou:** None. **E. Kavanagh:** None. **M. Bäck:** None. **P. Nilsson:** None. **B. Joseph:** None. **O. Hermanson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Celluminova.

Poster

592. Neuro-Oncology I

Location: Hall A

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Program#/Poster#: 592.23/I10

Topic: C.12. Neuro-Oncology

Support: AIRC 2014

Title: Pharmacological inhibition of CLIC1 chloride channel impairs glioblastoma stem cell proliferation

Authors: R. WURTH[1], F. BARBIERI[1], M. TONELLI[1], G. GAUDENZI[2], M. PERETTI[2], G. VITALE[2], M. MAZZANTI[2], *T. FLORIO[1];
[1]Univ. of Genova, Genova, Italy; [2]Univ. of Milano, Milano, Italy

Abstract: Glioblastoma (GBM) is the most common primary brain tumor in adults showing an overall survival of only 14.6 months, even in the presence of aggressive treatments. Thus, the discover of new drugs is a compelling requirement. Chloride intracellular channel 1 (CLIC1) is involved in development of GBM, controlling cell cycle progression in tumor cells. Here we show that metformin, the first-line drug for type-2 diabetes that recently showed to possess antitumor properties, selectively inhibits CLIC1 activity in human GBM stem cells (GSCs), leading to tumor cell growth arrest. The inhibition of CLIC1 conductance induced by metformin reduces GSC proliferation, causing arrest in G1 phase of the cell cycle. This effect is time-

dependent, and prolonged treatments lead to antiproliferative effects for low, clinically achievable, metformin concentrations. Single point mutation in the putative CLIC1 pore region impairs metformin modulation of the channel activity, suggesting that metformin binding site is located on the extracellular portion of CLIC1. Metformin's effects were also shown *in vivo*, causing a significant inhibition of GSC invasiveness and metastatic diffusion. Interestingly, CLIC1 is not active in mesenchymal stem cells, and consequently these cells are not affected by the antiproliferative effects of metformin, highlighting that this drug seem to be GSC-selective. These results identify a completely new molecular target for the antiproliferative effects of metformin, which could be exploited to identify novel pharmacological approaches for GBM. Following this line we evaluated the antitumor activity, and the ability to inhibit CLIC1 ion conductance, of several known and novel biguanide derivatives. In particular, we identified novel compounds showing higher potency than metformin, but reproducing the same mechanism of action, representing promising candidates to be further developed in clinical settings. Since the lack of drugs affecting GSCs viability is the main cause of therapy failure and tumor relapse, the identification of novel and specific molecular targets and of drugs acting on it represents a needed pharmacological strategy to improve GBM treatment.

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Poster

592. Neuro-Oncology I

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 592.24/I11

Topic: C.12. Neuro-Oncology

Title: Bioenergetic adaptation of invasive glioma: a complication to therapeutic targeting?

Authors: ***B. AHN**[1,2], Y. AHN[3], N.-H. DANG[1,2], A. WELJIE[4], J. RHO[3], D. SENGER[1,2]; [1]Dept. of Oncology, Univ. of Calgary, Calgary, AB, Canada; [2]Southern Alberta Cancer Res. Inst., Calgary, AB, Canada; [3]Dept. of Pediatrics, Univ. of Calgary, Calgary, AB, Canada; [4]Dept. of Pharmacol., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Patients with high-grade glioma or glioblastoma (GBM) have an average survival of only one year and existing therapies are palliative at best. Current therapeutic strategies include the exploitation of the tumor cellular metabolism and largely focuses on the higher rate of glucose consumption in the cancer cells as compared to the surrounding normal tissues, a phenomenon known as the Warburg effect. Recently, glioblastoma tumors have been shown, in

addition to glucose, to simultaneously oxidize acetate providing an explanation for the observed resistance of glioma cells to conventional metabolic drugs that target glycolysis. Herein, we provide evidence that the upregulation of glutamine metabolism can result in resistance to glycolytic pathway inhibitors (DCA, 2DG) or glucose oxidation targeting drugs (Metformin). Using previously established non-invasive (U87pc) and invasive (U87p75^{NTR}) human GBM cell lines, or patient-derived brain tumour initiating cells (BTICs), we found that highly invasive GBM cells are resistant to DCA, DG and Metformin, but not BPTES (an inhibitor of glutaminase). Moreover, we found that oxygen consumption (OCR; measure of oxidative phosphorylation) and extracellular acidification (ECAR; measure of cellular glycolytic activity) were higher in non-invasive GBM cells as compared to their invasive counterparts suggesting that invasive glioma cells are less dependent on glycolytic activity or oxidative phosphorylation. Conversely, metabolomic studies revealed that glutamine metabolism was elevated in the highly invasive GBM population, an observation that was associated with an increase in glutamine metabolism related genes. Consistent with this observation, the invasive glioma cells maintained the capacity to grow in the absence of glucose where the cells were shown to utilize glutamine as a metabolic substrate. These data highlight the bioenergetic diversity and adaptability of human glioma and provide data to support a role for glutamine metabolism in promoting resistance of the highly invasive population and thus identifies additional mechanisms for the development of therapeutic resistance.

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Poster

592. Neuro-Oncology I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 592.25/I12

Topic: C.12. Neuro-Oncology

Title: Differential tumor graft acceptance of 261 Glioblastoma Multitforme (GBM) cell lines between wild type C5Bl6, CD74 deficient, and Gamma Delta TCR deficient mice

Authors: ***S. MUKHERJEE**[1], L. DAO[1], R. TOBIN[1], G. DUSIO[2], E. FONKEM[4], M. NEWELL ROGERS[1,3];
[1]Surgery, Texas A & M, Temple, TX; [2]Surgery, [3]Scott and White Healthcare, Temple, TX; [4]Neurol., scott and White Healthcare, Temple, TX

Abstract: Background and Significance. Glioblastoma Multiforme (GBM) is a deadly and highly aggressive brain tumor with grim prognosis. At present none of the treatment strategies extend the life of most patients beyond a year. A contribution from the immune system in the control and/or growth of tumors is currently under intense investigation. However, the strategies GBM cells use to hide from the immune cells are poorly understood. Experimental Approach. To address this issue, we compared the tumor graft acceptance of 261 cells (mouse glioma cell line/derived from a tumor from a C5Bl6 strain background) into C5Bl6 mice with three genetic modifications (CD74, invariant chain knockout mice; gamma delta knockout mice; and control C5Bl6 mice). The 261 cells were injected stereotactically in the caudate nucleus and mice were observed for 4-6 weeks. Results. The data showed that the tumor acceptance in C5Bl6 mice was higher when compared to either CD74 deficient or Gamma Delta TCR deficient mice. In addition, C57Bl6 mice showed rapid tumor growth with robust neurological deficit as early as 4 weeks. No neurological deficit was observed in invariant chain deficient mice or gamma delta knockout mice. Conclusions. These data suggest a contribution from CD74 as well as gamma delta T cells in tumor graft acceptance. Further experiments are ongoing to determine the potential role of CD74 and/or gamma delta T cells in the progression of GBM.

Disclosures: S. Mukherjee: None. **L. Dao:** None. **R. Tobin:** None. **G. Dusio:** None. **E. Fonkem:** None. **M. Newell Rogers:** None.

Poster

592. Neuro-Oncology I

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Topic: C.12. Neuro-Oncology

Support: Mystic Force Foundation

ACC IAC Student Grant

Title: Glycolytic inhibition induces er stress and apoptotic cell death in patient derived glioblastoma stem-like cells

Authors: *S. S. SHAH[1,2], G. A. RODRIGUEZ[1], A. SANCHEZ[1], M. SCHECHTER[2], W. WALTERS[1], R. J. KOMOTAR[1], J. S. PRINCE[2], R. M. GRAHAM[1];
[1]Dept. of Neurolog. Surgery, Univ. of Miami Miller Sch. of Med., Miami, FL; [2]Dept. of Biol., UM Electron Microscopy Lab., Coral Gables, FL

Abstract: Background: Glioblastoma multiforme (GBM) is one of the most malignant and common primary brain tumors. Even with aggressive treatment, patient prognosis is dismal with a median survival time of 14.7 months. A subset of glioblastoma cells, glioblastoma stem cells (GSCs), is treatment resistant and implicated in disease recurrence. Currently, there is controversy regarding metabolic pathways GSCs employ_glycolysis versus oxidative phosphorylation. Therefore, we sought to perform transmission electron microscopic (TEM) analysis of GSC ultrastructure to determine metabolic preference, evaluate potential therapeutic targets, and propose mechanisms of action of novel treatments. Methods: GSCs were generated from patient-derived tumors, propagated in neurosphere media, and examined for stem-cell markers (Nestin, Musashi, Sox2, CD44, GFAP, BMI1) and ability to generate tumors in nude mice. Cellular morphology was evaluated by TEM. Effect of glycolytic inhibitors, 2-deoxyglucose (2-DG) and 3-bromopyruvate (3-BrPA), on cell viability was determined by MTS assay. Drug effect on cell signaling pathways was elucidated through Western Blot. Results: TEM analysis of multiple patient-derived GSCs confirmed a majority (>50%) of mitochondria exhibit either cristae loss or inner-fold polarization, indicating less available surface area for oxidative phosphorylation suggesting a metabolic dependence on glycolysis. Glycolytic inhibition significantly reduced GSC viability at 72 hours. 2-DG showed most consistent loss in viability compared to non-treated controls at clinically relevant concentrations (0.5mM = 52.1±10.3%; 1.0mM = 22.1±9.9%; 2.0mM = 8.1±5.0%). 3-BrPA showed similar dose dependent loss of GSC viability. In addition, 2-DG was found to up-regulate ER Stress markers (GRP78, CHOP) while also increasing apoptotic markers (cleaved PARP, cleaved Cas3). Conclusions: Targeting GSCs is vital in preventing tumor regeneration. EM provides a useful tool in developing experimental therapies. Our EM results indicate that oxidative phosphorylation is severely compromised in GSCs. Glycolytic inhibition proved effective in targeting GSCs and may represent an adjuvant therapy for a disease with minimal survival.

Disclosures: **S.S. Shah:** None. **G.A. Rodriguez:** None. **A. Sanchez:** None. **M. Schechter:** None. **W. Walters:** A. Employment/Salary (full or part-time):; University of Miami Brain Tumor Initiative. **R.J. Komotar:** F. Consulting Fees (e.g., advisory boards); Osteomed, LLC, Codman/Johnson&Johnson, Inc., Medtronic, Inc., Synaptive, Inc. **J.S. Prince:** A. Employment/Salary (full or part-time):; University of Miami. **R.M. Graham:** A. Employment/Salary (full or part-time):; University of Miami Brain Tumor Initiative.

Poster

592. Neuro-Oncology I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 592.27/I14

Topic: C.12. Neuro-Oncology

Support: R01-NS074387

R01-NS057711

R21-NS091555

MICHR Pilot R14 U040007

University of Michigan U042841

R01-NS054193

R01-NS061107

Title: The CXCL12/CXCR4 signaling axis in the pathogenesis and progression of neural stem cell derived glioblastomas

Authors: *A. CALINESCU[1], E. CARBALLO[2], D. B. ZAMLER[1], R. DOHERTY[1], D. TRAN[3], P. R. LOWENSTEIN[1,4], M. G. CASTRO[1,4];
[1]Neurosurg., [2]Med. Sch., [3]Sch. of Literature Sci. and Arts, [4]Cell and Developmental Biol., Univ. of Michigan, Ann Arbor, MI

Abstract: CXCL12 is a pleiotropic chemokine critical for the development and trafficking of immune cells, a key regulator of CNS development, neuronal survival and neurotransmission. Altered expression and function of CXCL12 is found in numerous infectious, autoimmune and malignant CNS pathologies like glioblastoma (GBM). In a screen of chemokines secreted by GBM cell lines we identified CXCL12 with highest expression in glioma cells derived from the malignant transformation of neural stem cells in neonatal mice. Tumors were induced with oncogenic DNA (NRAS and SV40-LgT) injected into the lateral ventricles of P1 mice. Transformed cells proliferate from the ventricles towards the brain parenchyma or travel alongside CXCL12 + vascular endothelial cells to form supra-tentorial tumors in the cortex, striatum or hippocampus. These tumors express the neural stem cell marker Nestin and the glioma stem cell marker Olig2 and render animals moribund within 30 days. Mature tumors harbor the histological hallmarks of human GBM (WHO grade IV): pseudo-palisading necrosis, nuclear atypias, microvascular proliferation and glomeruloid vascular abnormalities. Treatment with Plerixafor, a CXCR4 inhibitor, the cognate signaling receptor for CXCL12, extends the median survival of tumor bearing animals to 53 days ($p=0.0006$). Cell lines derived from these tumors show a 6-fold increase in expression of CXCL12 after 96 hours in culture, which is completely blocked by Plerixafor and correlates with decrease in cell cycle progression, expression of cyclin D1, cdk4 and cdk6. This is preceded at 72h by a decrease in Rb protein and increase in apoptosis. Within the tumor, expression of CXCR4 is maximal in tumor infiltrating myeloid derived suppressor cells (MDSCs), a heterogeneous population of immature bone

marrow (BM) derived cells which suppress the antitumor immune responses in numerous cancers. Treatment of BM cells with GBM conditioned media induces expansion of MDSCs which is dose-dependently inhibited by Plerixafor. Migration and invasion of MDSCs towards CXCL12 is completely blocked by Plerixafor. *In vivo* experiments currently underway explore the role of the CXCL12/CXCR4 signaling axis in tumor infiltrating MDSCs using a genetic mouse model in which CXCR4 is ablated in this population. Our data so far illustrate that in neural stem cells derived GBMs the CXCL12/CXCR4 axis operates via an autocrine positive feedback mechanism in which CXCL12 induces its own expression towards promoting survival and cell cycle progression. The increased survival of immunocompetent tumor bearing animals treated with the CXCR4 inhibitor may result from a concerted effect on tumor cells and MDSCs.

Disclosures: A. Calinescu: None. **E. Carballo:** None. **D.B. Zamler:** None. **R. Doherty:** None. **D. Tran:** None. **P.R. Lowenstein:** None. **M.G. Castro:** None.

Poster

592. Neuro-Oncology I

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 592.28/I15

Topic: C.12. Neuro-Oncology

Support: PRA_2015_0083

Title: Carnosol: a natural approach to control cancer stem cell in human neuroblastoma and glioblastoma

Authors: C. GIACOMELLI[1], M. L. TRINCAVELLI[1,2], S. DANIELE[1], A. BERTOLI[1], G. FLAMINI[1], A. BRACA[1,2], *C. MARTINI[1,2];
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Abstract: Carnosol is a naturally diphenolic diterpene found in rosemary that possess anti-inflammatory and anti-cancer effects, although the molecular mechanisms of its activity remain poorly investigated. Neuroblastoma (NB), an extracranial nervous system tumor, and Glioblastoma Multiforme (GBM), a glial tumor with a high proliferation rate and resistance to chemotherapy, are two aggressive cancer characterized by poor prognosis. Recently, several studies have shown the importance of a minor population of cells with stem-like properties (cancer stem cells, CSCs) for the etiopathogenesis and progression of brain tumors. This effect has been related to CSCs self-renewal capacity, tumorigenicity, and altered expression of

specific molecules such as the constitutive activation of signal transducer and activator of transcription 3 (STAT3) signaling (Magee et al., 2012; Zhou et al., 2014). Furthermore, they play a role as master regulators not only in the development of different cancer but also during the process of chemoresistance acquisition. Recently, it has been reported that carnosol is able to induce apoptosis in different tumor through the regulation of intracellular signaling pathways such as nuclear factor kappa B (NFκB), Akt/mTOR and STAT3 inactivation (Park et al, 2014). Herein, we investigate the effect of carnosol in survival of NB, GBM and the respective CSCs. Interestingly, the treatment caused a significant anti-proliferative effect on NB and GBM cells, and a reduction of the CSC proliferation. The effects were ascribed to both the induction of apoptosis and the blocking of cell cycle. Most importantly, carnosol produced synergic/addictive effects on cell apoptosis to the genotoxic action of temozolomide (TMZ) and reduced the ability of cells to recover cell growth. Globally, these data highlighted the potential use of natural diterpenes as starting point in the development of drugs for the treatment of NB and GBM. Moreover, carnososl could represent a promising natural approach to sensitize cancer stem cells to conventional chemotherapy (TMZ). Magee, J.A.; Piskounova, E.; Morrison, S.J.; Cancer stem cells: Impact, heterogeneity, and uncertainty. Cancer. Cell. 21:283-296; 2012. Zhou, J.; Yi, L.; Ouyang, Q.; Xu, L.; Cui, H.; Xu, M.; Neurotensin signaling regulates stem-like traits of glioblastoma stem cells through activation of IL-8/CXCR1/STAT3 pathway. Cell. Signal. 26(12):2896-902; 2014. Park, K.W.; Kundu, J.; Chae, I.G.; Kim, D.H.; Yu, M.H.; Kundu, J.K.; Chun, K.S.; Carnosol induces apoptosis through generation of ROS and inactivation of STAT3 signaling in human colon cancer HCT116 cells. Int. J. Oncol. 44(4):1309-15; 2014.

Disclosures: **C. Giacomelli:** None. **M.L. Trincavelli:** None. **S. Daniele:** None. **A. Bertoli:** None. **G. Flamini:** None. **A. Braca:** None. **C. Martini:** None.

Poster

592. Neuro-Oncology I

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Topic: C.12. Neuro-Oncology

Support: NIH Grant T32GM007518

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Title: The role of neuropilin 1 in glioma associated microglia and macrophages

Authors: *J. MIYAUCHI[1], J. NISSEN[1], D. SELWOOD[2], S. TSIRKA[1];
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Abstract: Malignant gliomas are the most commonly diagnosed tumors of the central nervous system (CNS). Despite management, median time of survival after diagnosis falls between 12 to 15 months. Current treatment modalities are suboptimal and there is a substantial need to develop more effective therapies. Modulation of the immune system is a promising strategy as innate and adaptive immunity play important roles in cancer progression. Neuropilin 1 (Nrp1), is responsible for amplifying pro-angiogenic signaling within the tumor microenvironment and its expression correlates with glioma malignancy. Nrp1 also signals via additional pathways and plays a role in the behavior of innate immune cells. Microglia, the resident macrophages of the CNS, can comprise over 30% of the cells in glioma biopsies. Gliomas secrete cytokines which suppress the anti-tumorigenicity of microglia, causing them to secrete factors that support the tumor's spread and growth. Some of the factors which are secreted by gliomas in high amounts signal via Nrp1 and its co-receptors. The objective of this research is to identify how Nrp1-mediated signaling in microglia affects glioma progression. Using a Cre-lox system, we generated mice which lack expression of Nrp1 in microglia and macrophages (MG/MPs). We demonstrate in an *in vivo* orthotopic glioma model, that tumors exhibit less vascularity, grow at a slower pace, and are populated by MG/MPs which exhibit a more anti-tumorigenic phenotype in mice that lack Nrp1 in MG/MPs or that are treated with a small molecule inhibitor of Nrp1. We conclude that ablation or pharmacologic inhibition of Nrp1 promotes an anti-tumorigenic shift in the phenotype of MG/MPs, effectively reducing tumor growth.

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Poster

593. Schizophrenia: Circuitry Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: Neuroscience Training Grant 5T32GM008471-19

Wallin Neuroscience Discovery Fund

NSF CAREER 1135581

NIH R01 MH077779

Title: Reduced functional connectivity and synchrony between spiking neurons in a primate model of schizophrenia

Authors: *J. L. ZICK[1,2], R. K. BLACKMAN[1,2,4], M. V. CHAFEE[1,4], T. I. NETOFF[3,1]; [1]Neurosci., [2]Med. Scientist Training Program (MD/PhD), [3]Biomed. Engin., Univ. of Minnesota, Minneapolis, MN; [4]Brain Sci. Center, VA Med. Ctr., Minneapolis, MN

Abstract: Disordered connectivity appears to be a key pathophysiological feature of schizophrenia. Measures of temporal correlation between regions of the brain are consistently reduced in schizophrenic patients upon functional imaging; however, evidence for functional disconnection at the synaptic level is limited. Here we describe a study in which we assessed functional connectivity between spiking neurons in a pharmacological nonhuman primate model of schizophrenia. Neural data were obtained from multielectrode recording arrays inserted into the parietal and prefrontal cortices of macaque monkeys while the animals performed a cognitive control task that measures a specific cognitive impairment in human patients with schizophrenia. Phencyclidine (PCP), an NMDA receptor (NMDAR) antagonist with well-described schizomimetic properties, was administered systemically on alternating days with injections of saline.To characterize changes in synaptic communication between neurons in the disease state, we first employed a Generalized Linear Model (GLM) approach to infer functional connectivity between neurons. Unlike traditional cross-correlation approaches used for inferring functional connectivity, GLMs parse out the proportion of variance in spike timing attributable to synaptic interactions between neurons from other sources of variance such as stimulus input, the intrinsic spike patterns of the cells, and the effects of other simultaneously-recorded cells in the network. After identifying functionally coupled pairs of neurons using GLMs, we evaluated the effects of PCP on functional coupling and synchrony between coupled cells. We found a dramatic decrease in the proportion of cells that were functionally coupled in the prefrontal cortex in the PCP condition as compared to the control condition. In order to investigate hypothesized alterations in spike timing in the disease state, we identified the distribution of interspike intervals between putative pre- and postsynaptic neurons. In our analysis we found a prominent “zero-lag” peak representing a large number of coincident (within 1 millisecond) action potentials between coupled cells in the saline condition, but not in the PCP condition. This suggests a change in the timing of action potentials which was apparent in the absence of a change in firing rates, precluding overall decreased activity as an explanation for reduced synchrony. In summary, these results suggest that PCP induces a functional disconnection between synaptically coupled cortical neurons which may be related to a Hebbian reduction in synaptic strength resulting from desynchronization of spiking activity.

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Poster

593. Schizophrenia: Circuitry Models

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Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Ketamine induced chronic alterations of neural oscillatory amplitudes and cross-frequency couplings in the rat hippocampus: a translational model of schizophrenia

Authors: *T. I. MICHAELS, L. L. LONG, J. J. CHROBAK, C.-M. A. CHEN, C.-M. A. CHEN;
Dept. of Psychology, Univ. of Connecticut, Storrs, CT

Abstract: Disrupted neuronal oscillations have been identified as a possible neural mechanism for the perceptual and cognitive symptoms of schizophrenia. Although findings from human research have focused on abnormalities in different frequency band oscillations, emerging evidences suggest that interactions between different frequency bands, cross-frequency coupling (CFC) serve an important role in integrating sensory and cognitive information and may contribute to the pathophysiology of schizophrenia. Animal studies have utilized ketamine as a pharmacological model of disrupted neuronal oscillations, but few studies have examined its effects on cross-frequency couplings. In the present study, we investigated the acute and chronic effects of ketamine (30 mg/kg i.p. each day) versus saline on changes in averaged amplitudes in different frequency bands (i.e., theta: 6-12 Hz, slow gamma: 25-50 Hz, and fast gamma: 65-100 Hz) and modulations in low-frequency phase (1 to 30 Hz) and high frequency amplitude (50 to 115 Hz) couplings in the rat hippocampus over a 14-day period. We hypothesize that there would be both acute and chronic ketamine effects on: 1) oscillatory amplitudes in theta and gamma frequency bands, and 2) CFC. Electrode recordings were conducted while the rats were running in a four-arm maze. Results indicate a significant drug-by-day interaction effect for both gamma ($F(2, 172) = 3.75$, $p = 0.03$) and theta ($F(2, 172) = 4.64$, $p = 0.01$) amplitude. Within the ketamine group, there was a gradual decrease in fast gamma amplitude from day 1 to day14 and an increase in theta amplitude from day 1 to day 7. Ketamine administration also induced acute and chronic alterations in the strength of phase-amplitude coupling that were not observed in the saline group. Our results demonstrate that chronic ketamine administration alters the interaction of low-frequency phase and high-frequency oscillations in the rat hippocampus. These findings are consistent with human studies and provide evidence that CFC may serve as an important neuronal mechanism for cognitive and perceptual processes known to be impaired in schizophrenia.

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Poster

593. Schizophrenia: Circuitry Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 593.03/I19

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: ETH Research Grant ETH-25_13-2

Title: Gut vagal afferents modulate schizophrenia-relevant behavioral functions

Authors: ***M. KLARER**[1], M. ARNOLD[1], J.-P. KRIEGER[1], W. LANGHANS[1], U. MEYER[1,2]; [1]Physiol. and Behavior Lab., ETH Zurich, Schwerzenbach, Switzerland; [2]Inst. of Pharmacol. and Toxicology, Univ. of Zurich-Vetsuisse, Zurich, Switzerland

Abstract: Vagal afferents are an important neuronal component of the gut-brain axis allowing bottom-up information flow from the viscera to the CNS. Impaired vagal signaling has been implicated in a number of neuropsychiatric disorders, including anxiety disorders, major depression and schizophrenia. We have recently shown that innate anxiety and learned fear are both subjected to visceral modulation through abdominal vagal afferent signaling (Klarer et al., 2014, J Neurosci 34:7067-7076). Here, we explored whether vagal afferents may further modulate behavioral functions relevant to schizophrenia and related psychotic disorders. To this end, we used a rat model of subdiaphragmatic vagal deafferentation (SDA), the most complete and selective vagal deafferentation method existing to date, to study the consequences of complete disconnection of abdominal vagal afferents on sensorimotor gating selective attention, and sensitivity to dopamine-stimulating drug challenge. We found that SDA-induced loss of vagal afferent signaling led to impairments in prepulse inhibition (PPI) of the acoustic startle reflex and latent inhibition (LI) in conditioned taste aversion. Compared with Sham controls, SDA rats also displayed increased stereotyped behavioral responses to systemic treatment with the indirect dopamine receptor agonist amphetamine (2 mg/kg, i.p.). Post-mortem immunohistochemical investigations revealed increased tyrosine hydroxylase densities in the dorsal (but not ventral) striatum of SDA rats relative to Sham controls. Our study demonstrates that gut vagal afferents modulate behavioral functions implicated in schizophrenia and related psychotic disorders, possibly via changing striatal dopaminergic signaling. These data are in line with the beneficial effects of vagus nerve stimulation against schizophrenia-relevant abnormalities (Perez et al., 2014, J Neurosci 34:9261-9267) and add further weight to theories

emphasizing an etiopathological role of impaired afferent visceral signaling in psychosis-related disorders.

Disclosures: **M. Klarer:** None. **M. Arnold:** None. **J. Krieger:** None. **W. Langhans:** None. **U. Meyer:** None.

Poster

593. Schizophrenia: Circuitry Models

Location: Hall A

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Program#/Poster#: 593.04/I20

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: P51OD11132

Title: Sub-anesthetic ketamine-induced changes in resting state functional connectivity in conscious nonhuman primates

Authors: ***E. MALTBIE**[1], K. GOPINATH[1], N. URUSHINO[1], L. HOWELL[2];
[1]Emory Univ., Atlanta, GA; [2]Emory Univ., Atlanta, Georgia

Abstract: There is significant interest in the NMDA-receptor antagonist ketamine due to its efficacy in treating depressive disorders and its ability to induce psychotic-like symptoms that make it a useful tool for modeling psychosis. This study extends previous research using fMRI to determine ketamine-induced brain activation in conscious nonhuman primates as a translational model for evaluating antipsychotics. Five adult female rhesus monkeys received a bolus i.v. infusion of 0.345 mg/kg ketamine followed by continuous i.v. infusion of 0.256 mg/kg/hr ketamine. All subjects were responsive to tactile and auditory stimulation, indicating that dosing was well below the anesthetic range. Subjects were scanned in a Siemens Trio 3T magnet while laying prone in a custom built MRI cradle fitted to a transmit-receive volume head coil designed specifically for nonhuman primates. BOLD fMRI images were collected utilizing a whole-brain gradient echo single-shot echo planar imaging sequence (TR/TE/FA = 3000ms/32ms/90; 1.5mm isotropic resolution). Each subject underwent 3 separate scans: a 10-minute baseline scan and two ketamine infusion scans, with and without risperidone pretreatment (0.06 mg/kg) one hour prior to scanning. Ketamine-induced changes in functional connectivity were assessed by seed-based cross correlation analysis comparing each ketamine scan against the baseline scan. Spherical 3mm seed regions defined a priori were placed in the amygdala, subgenual cingulate, medial dorsal thalamus, dorsolateral and medial prefrontal cortex (dlPFC and mPFC), orbitofrontal cortex (OFC), anterior and posterior cingulate cortex (ACC and PCC), and ventral

striatum. Ketamine induced robust functional connectivity increases in limbic-cortical and cortico-striatal networks involved in emotional regulation, motivation, and executive function. The subgenual cingulate displayed increased connectivity with mPFC, dlPFC, inferior temporal gyrus, and amygdala. The amygdala showed increased connectivity with mPFC, OFC, and dorsal striatum. The ventral striatum displayed increased connectivity with mPFC and dlPFC. Pretreatment with the antipsychotic drug risperidone blocked ketamine-induced increases in each of these networks. These data are consistent with literature in humans showing that ketamine induces hyperconnectivity in the prefrontal cortex (early schizophrenia) and acutely modulates connectivity in networks implicated in mood disorders. The model employed has significant translational value in medications development.

Disclosures: E. Maltbie: None. **K. Gopinath:** None. **N. Urushino:** None. **L. Howell:** None.

Poster

593. Schizophrenia: Circuitry Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 593.05/I21

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIH Grant M086518

Title: Knockout of NR1 receptors in the reticular nucleus of the thalamus impairs reversal learning and decreases sleep spindles

Authors: *T. E. BJORNESS[1], S. BIRNBAUM[2], J. LISMAN[3], R. W. GREENE[2];
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Abstract: The reticular nucleus of the thalamus (nRT) receives widespread input from the cortex and the thalamus and in turn provides GABAergic inhibitory projections throughout the thalamus including thalamic relay neurons that project to the cortex. Activity in the nRT is thought to be important for sensory gating, a function impaired in schizophrenia. Additionally, spindle activity during sleep is dependent on burst firing of neurons in the nRT and is decreased in schizophrenics. Disruption of normal activity in the nRT has been posited as a possible source of schizophrenia-related symptoms. In the current experiment, NR1 NMDA receptors were locally knocked out through the use of AAV-Cre injections into the nRT of male floxed NR1 mutant mice. AAV-GFP injections into the nRT were used as a control. Briefly, approximately one microliter of AAV-Cre or AAV-GFP was injected bilaterally into the nRT using a Picospritzer

injection system. A subset of mice was also implanted with skull screw electrodes for electroencephalography and paddle electrodes into the nuchal muscle for electromyography. Mice were given at least 2 weeks for recovery from surgical procedures prior to the start of behavioral experiments, which consisted of Y maze reversal learning, nest building assessment, social transmission of food preference, fear conditioning, and polysomnography. For polysomnography, EEG and EMG signals were recorded under undisturbed baseline conditions for 72 hours, after which sleep state was assigned using standard criteria. Additionally, spindles were identified and counted using a custom Matlab module. Local knockdown of NR1 receptors in the nRT resulted in an impairment in reversal learning, while training and testing on the Y maze was not affected. Additionally, AAV-Cre injected mice showed a lack of normal nest building. Conversely, social transmission of food preference and fear conditioning were not different than controls. When we investigated the effect of NR1 knockdown in the nRT on sleep/waking behavior, we found that although there was a similar amount of time in sleep/waking states as compared to controls, frequency of peak EEG power during waking slowed from 8 Hz in the theta range to 4 Hz in the delta range. Furthermore, AAV-Cre injected mice showed a profound decrease in the number of spindles during SWS, along with a decrease in average spindle frequency. In sum, these results support a possible role for thalamic NMDA-related dysfunction in mediating some of the symptoms of schizophrenia, in particular that of impaired reversal learning and decreased spindle activity which has previously been reported in schizophrenics.

Disclosures: **T.E. Bjorness:** None. **S. Birnbaum:** None. **J. Lisman:** None. **R.W. Greene:** None.

Poster

593. Schizophrenia: Circuitry Models

Location: Hall A

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Program#/Poster#: 593.06/I22

Topic: A.09. Adolescent Development

Support: NHMRC grant 1042259

UQ international scholarship

Queensland NMR Network

Title: The short- and long-term behavioural effects of chronic risperidone differ in adolescents and adults

Authors: *A. MOE[1], S. ALEXANDER[1], N. D. KURNIAWAN[2], X. CUI[1], T. H. J. BURNE[1,3], D. W. EYLES[1,3];
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Abstract: Adolescent brain undergoes major remodelling changes in several neural pathways, raising the possibility of vulnerability to exogenous pharmacological agents. Studies in adult humans and animals have shown that the maturing neurotransmitter systems of the adolescent brain such as dopamine systems and brain structure can be adversely affected by antipsychotic drugs (APDs). However, the dramatic rise in APD prescription to adolescents over the recent decades has not been accompanied by a parallel increase in knowledge on the APDs' effects on the adolescent brain, especially long-term outcomes. Our study tested the hypothesis that the adolescent brain is selectively sensitive to APDs, by examining the well-known effects of APDs on suppression of the conditioned avoidance responses (CAR) in adolescent and adult rodents. Male rats achieving ≥70% avoidance were subjected to chronic 21-day treatment with 1.3 mg/kg risperidone or vehicle either as adolescents (postnatal day (P) 35-55)) or as adults (P80-100). In both age groups, CAR was examined both during chronic treatment (day 1 and 17 of APD exposure) and after lengthy drug-free interval (at P118 for both age groups). At P120, the long-term effects on neural metabolites in nucleus accumbens and brain structures were examined with *in vivo* nuclear magnetic resonance spectroscopy (MRS) and structural MRI respectively, with all brain tissues collected at P127. Similar CAR responses were observed in adolescents and adults on day 1 of chronic treatment. On day 17, adolescent risperidone treatment induced less suppression of CAR and produced fewer escape failures and higher crossings, compared to the adult risperidone treatment. At P118, i.e. after drug-free interval, a long-term sensitization to the CAR-suppressive effects of risperidone was observed selectively in the adolescent risperidone-exposed rats. The underlying neurochemical and structural changes are still under active investigation. Our differential age-dependent behavioural responses both during chronic treatment and after drug washout suggest that the effect of risperidone on the immature adolescent brain is different from that on adult brain. More importantly, the finding that only adolescent-treated rats developed long-term sensitized response further suggests a higher sensitivity of the adolescent brain to risperidone's long-term effects. Differential neural adaptation changes following chronic risperidone exposure are speculated to occur in adolescents and adults during drug-free interval. Given risperidone is the most commonly used atypical APD in adolescents, our findings may have clinical implications.

Disclosures: A. Moe: None. **S. Alexander:** None. **N.D. Kurniawan:** None. **X. Cui:** None. **T.H.J. Burne:** None. **D.W. Eyles:** None.

Poster

593. Schizophrenia: Circuitry Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 593.07/I23

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NIH Grant MH57440

Title: Nucleus reuniens regulation of ventral tegmental area dopamine neuron activity

Authors: *E. C. ZIMMERMAN[1], N. JAKOBOWSKI[2], A. A. GRACE[2];
[1]Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; [2]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Dopamine (DA) neurons of the ventral tegmental area (VTA) mediate a wide variety of fundamental behaviors, ranging from reward to motivation and salience. Previous findings from our group and others have described a tripartite circuit composed of the ventral subiculum (vSub), nucleus accumbens (NAc), and ventral pallidum (VP), which governs the proportion of VTA DA neurons that are spontaneously active, ie "population activity." Burst firing is believed to be the behaviorally relevant output of the DA system. However, population activity is a key parameter of VTA activity, because DA cells can only exhibit burst firing if they are spontaneously active. Therefore, the population activity acts as the "gain" to the burst firing "signal." However, all of the regions that modulate population activity have not been fully characterized. Several anatomical studies have described dense, reciprocal connections between vSub and the nucleus reuniens of the midline thalamus (RE). This suggests that RE could be involved in controlling VTA DA neuron population activity, but physiological studies examining this possibility are lacking. To address this question, male Sprague-Dawley rats were anesthetized with chloral hydrate. We then infused NMDA or vehicle into RE, and performed *in vivo* extracellular single-unit recordings of spontaneously active VTA DA neurons. Three properties of identified DA neurons were measured: population activity, quantified as the average number of spontaneously active cells per electrode track, average firing rate, and percent of spikes occurring in bursts. We found that NMDA activation of RE increased population activity in VTA DA neurons without affecting firing rate or burst firing. These findings suggest that RE could play a key role in modulating hippocampal control of VTA DA neuron population activity.

Disclosures: E.C. Zimmerman: None. **N. Jakobowski:** None. **A.A. Grace:** None.

Poster

593. Schizophrenia: Circuitry Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 593.08/I24

Topic: C.19. Drug Discovery and Development

Title: Identification of EEG biomarkers in mouse models of psychiatric disorders induced by NMDA antagonists

Authors: *V. DUVEAU, C. TOULLER, B. POUYATOS, C. DUMONT, C. BOUYSSIÈRES, Y. ROCHE, C. ROUCARD;
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Abstract: EEG and related methodologies have emerged as powerful tools in both clinical and preclinical research programs for the identification of physiological and pathological biomarkers. Nowadays EEG endpoints are largely used in the clinic to identify and evaluate a pathological state and/or as surrogate biomarkers for clinical trials (depression, schizophrenia, autism, epilepsy ⋯). EEG biomarkers are easily translatable from human to rodent offering a unique opportunity to develop more efficient drug discovery programs. Two main types of EEG activities can be recorded: spontaneous and evoked. Spontaneous EEG activity is recorded continuously in behaving animals whereas evoked activities are recorded after sensory stimulations (auditory, visual etc⋯). In rodents, EEG responses evoked by auditory stimulation (AERPs) can be recorded in the cortex or the hippocampus. They are composed of a succession of positive and negative deflections of variable latencies corresponding to the treatment of information by the ascending auditory pathways. A second level of signal analysis can be performed by measuring the power of gamma oscillations evoked by the stimulations, as well as the inter-trial phase coherence (ITC) of this gamma response. The gamma band is of special interest in neurological and psychiatric disorders as it is linked to the integration and processing of information. In this work, we studied the alterations of AERP responses and the associated impairment in the gamma band power and ITC index in well-known mouse models of psychiatric disorders induced by NMDA antagonists (MK801 and ketamine). The goals of these recordings were (1) to define the EEG signatures of these animal models, and (2) to assess their use as potential biomarkers of these diseases. In C57Bl6 mice, the AERP response is typically composed of a positive deviation at 20-30ms (P1) followed by a prominent notch at 40-60ms (N1) and a late positive peak at around 100-200ms (P2). Ketamine and MK801 both altered the AERP responses, but with different patterns. While Ketamine induced dose-dependent decreases of the N1 and P2 amplitudes, MK801 caused both a decrease of amplitude and an increase of latency of both these deviations. These drugs left the P1 deviation unaffected. The evoked gamma power and ITC indexes were, for their part, impaired dose-dependently by the MK801 only. In this study, we identified functional biomarkers in mouse models of psychiatric disorders induced by NMDA antagonists using EEG and related methodologies. These specific biomarkers

could represent an important tool for the identification, selection and validation of new innovative therapeutics in psychiatric disorders.

Disclosures: **V. Duveau:** None. **C. Touller:** None. **B. Pouyatos:** None. **C. Dumont:** None. **C. Bouyssières:** None. **Y. Roche:** None. **C. Roucard:** None.

Poster

593. Schizophrenia: Circuitry Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 593.09/I25

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: APA Dissertation Research Award

Title: Chronic ketamine administration differentially alters parvalbumin expression as a function of age and time of sacrifice: evidence for dynamic protein expression

Authors: *J. A. CORRIVEAU, K. M. KEARY, III, V. M. KANIA, M. M. CHALUPARAMBIL, J. J. CHROBAK;
Psychology, Univ. of Connecticut, Storrs, CT

Abstract: A marked decrease in the expression of the calcium-binding protein (CBP) parvalbumin (PV) has been a consistent postmortem finding in schizophrenia. This reduction in CBP immunoreactivity is specific to PV, with alterations exclusively seen in the prefrontal cortex and hippocampus of patients. Rodent models of NMDA-receptor hypofunction utilizing non-competitive NMDA antagonist drugs (e.g. ketamine) to induce schizophrenic-like cognitive impairments show a comparable decrease in PV immunoreactivity, which is often considered a marker of underlying neuropathology. However, previous studies looking at the effects of chronic ketamine administration on cognitive impairment and concomitant changes in PV expression are contradictory, with findings suggesting decreased, increased, or even no change in PV expression. Upon examination of the procedures used across studies it is clear that there many inconsistencies, particularly with regard to the age of animals used, as well as the timeline of tissue collection. In order to better understand the possibility of methodological differences impacting PV expression, the present study examined the impact of age and time of sacrifice in behaviorally-naïve male Sprague-Dawley rats following chronic ketamine treatment (14 consecutive days of 30 mg/kg IP ketamine). Our findings suggest a dynamic interaction between age and time of sacrifice on prefrontal cortical and hippocampal PV expression based on treatment. Based on our data, we propose that PV expression is a highly dynamic marker, and

that changes in expression following NMDA antagonist treatment should be considered in the context of the age of the animals used, as well as the timeline of experimental procedures.

Disclosures: J.A. Corriveau: None. **K.M. Keary:** None. **V.M. Kania:** None. **M.M. Chaluparambil:** None. **J.J. Chrobak:** None.

Poster

593. Schizophrenia: Circuitry Models

Location: Hall A

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Program#/Poster#: 593.10/I26

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: INP Grant 123240.1

CONACYT Grant 129303

Title: Subcortical coherence changes induced by high-frequency stimulation in the thalamic reticular nucleus on a neonatal model of schizophrenia

Authors: *G. CONTRERAS-MURILLO[1], V. M. MAGDALENO-MADRIGAL[1], A. VALDÉS-CRUZ[1], R. FERNÁNDEZ-MAS[1], S. ALMAZÁN-ALVARADO[1], D. MARTÍNEZ-VARGAS[1], I. CAMACHO-ABREGO[2], J. V. NEGRETE-DÍAZ[2], G. FLORES[2];
[1]Lab. de Neurofisiología del Control y la Regulación, Inst. Nacional De Psiquiatría Ramón De La Fuen, Ciudad De México, Mexico; [2]Lab. Neuropsiquiatría, Benemérita Univ. Autónoma de Puebla, Puebla, Mexico

Abstract: Schizophrenia is a chronic and disabling psychiatric disorder that is often refractory to treatment. The heuristic model most thoroughly characterized is the neonatal ventral hippocampal lesion (NVHL). With this model, brain oscillations changes have been reported similar to schizophrenic patients. Deep brain stimulation (DBS) is accepted as an alternative therapy to treat a variety neuropsychiatric disorders refractory to conventional treatments. In this study high-frequency stimulation (HFS) of the thalamic reticular nucleus (TRN) was performed in the NVHL model of schizophrenia. Fourteen female Sprague-Dawley rats were used. Lesions of the ventral hippocampus in pups with ibotenic acid were performed in seven rats. Left seven rats were sham-operated. At time of implantation the rats were 3-4 months old and weighted ~215-270 g. Bilateral stainless steel electrodes were implanted in TRN (AP -1.4, L 1.8, H 6.2) thalamic dorsomedial nucleus (DM) (AP 1.4, L 1.3, H 5.4) and prelimbic area (PrL) (AP 3.0, L 0.6, H 3.6). Rats were classified as follows: Sham group and NVHL group, both groups received

bilateral HFS in TRN during one hour (100 Hz, 100 microsec pulses, 200 microA). Intra- and inter-hemispheric EEG recordings were analyzed. All animals showed a sudden behavioral arrest accompanied by widespread symmetric bilateral paroxysmal-like EEG activity. The DBS-TRN induced a significant increase in the coherence power of TRN/PrL, TRN/DM and DM/Prl ($p< 0.001$) at 0-4Hz and in the 35-55Hz bandwidth frequencies of the Sham group of left and right hemispheres. The interaction between the TRN and the DM increased with the DBS-TRN at 0-4Hz bandwidth frequency. In addition, in the interaction between the TRN, the DM with the PrL a significant decrease was observed ($p< 0.001$) in NVHL group, whereas the interaction between the TRN and the DM increased with the DBS-TRN and the interaction between TRN and the PrL decreased at 35-55 Hz bandwidth frequency. Our results suggest that HFS in TRN may modify functional connectivity between different parts thalamo-cortical network of NVHL rats, and provide experimental support for the concept that this thalamic region may be a promising target for focal stimulation to treat the refractory schizophrenia disorder.

Disclosures: G. Contreras-Murillo: None. **V.M. Magdaleno-Madrigal:** None. **A. Valdés-Cruz:** None. **R. Fernández-Mas:** None. **S. Almazán-Alvarado:** None. **D. Martínez-Vargas:** None. **I. Camacho-Abrego:** None. **J.V. Negrete-Díaz:** None. **G. Flores:** None.

Poster

593. Schizophrenia: Circuitry Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 593.11/I27

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Possible role for thalamic GAD67 in vacuous chewing movements

Authors: *S. E. BACHUS;
Psychology, George Mason Univ., Fairfax, VA

Abstract: We have previously found a significant negative correlation between levels of thalamic GABA-A alpha 1 mRNA and chronic haloperidol (HAL)-induced vacuous chewing movements (VCM), a rat model for tardive dyskinesia (Sharma et al., SfN Abstr. 2008). Thus, we have explored thalamic levels of GAD67 mRNA, as a presynaptic indicator of GABA function in thalamus. Group-housed male Long-Evans rats (starting wts 90-165 g) were monitored for 2 min samples weekly, under conditions in which environmental noise was not controlled for ("random noise"), over 7 wk, for baseline VCM, and then for 24 wk during chronic administration of HAL decanoate (28.5 mg/kg/ml, i.m., at 3 wk intervals; n=38) or vehicle (sesame oil; n=18), under random noise conditions, and subsequently also under

controlled quiet and noisy conditions. Upon completion of HAL, brains were frozen and cryosectioned onto slides for *in situ* hybridization with an oligoprobe complementary to GAD67 mRNA (or control probe) in diencephalic sections. Measurements of thalamic GAD67 mRNA levels were sampled from scanned and calibrated autoradiograms by a blinded observer. VCM were significantly higher under both random noise and noisy conditions, relative to quiet conditions, in the HAL-treated rats, with much higher variability occurring under the random noise condition relative to the noisy condition. There was a trend toward a reduction in thalamic GAD67 mRNA produced by chronic HAL ($t=1.89$, $p=.06$). Thalamic GAD67 mRNA was not significantly correlated with previously measured GABA-A alpha 1 mRNA in this cohort, among either controls or HAL-treated rats. Nonetheless, thalamic GAD67 mRNA was significantly positively correlated with VCM, specifically under the random noise condition ($r=.32$, $p=.025$), in which variability was highest. That is, the HAL-induced reduction in thalamic GAD67 occurred preferentially among the rats that were less sensitive to the enhancement of VCM by random noise. We conclude from this that effects of chronic HAL on thalamic GABA release may play a protective role against VCM, possibly via secondary upregulation of postsynaptic receptors.

Disclosures: S.E. Bachus: None.

Poster

593. Schizophrenia: Circuitry Models

Location: Hall A

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Program#/Poster#: 593.12/I28

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NRF Grant 2013R1A1A2013516

Title: Longitudinal observations of neuro-metabolites in social isolation rearing model: 1H-MRS study at 9.4 T

Authors: *H. HEO, H. H. LEE, H. KIM;
Seoul Nat'L Univ. Col. of Med., Seoul, Korea, Republic of

Abstract: The pathophysiology of schizophrenia is known to be associated with the imbalance between glutamate (Glu) and gamma-aminobutyric acid (GABA) levels. However, little is understood as to how this neuro-metabolic imbalance is initiated. In this study, Glu and GABA as well as other key brain metabolites were quantified *in vivo* in the left hippocampus of a group housing (GH) and a social isolation (SI) rearing rat models by using proton magnetic resonance

spectroscopy (1H-MRS) at 9.4T at the 6th, 10th and 14th week after the weaning period. SI models demonstrated diverse behavioral and neurochemical abnormalities that resembled the features of schizophrenia. The GABA to total creatine (tCr) ratio (GABA/tCr) and the N-acetylaspartate (NAA) to tCr ratio (NAA/tCr) were significantly lower in SI rats with respect to those of GH rats at the 10th and 14th week of isolation. However, Glu/tCr and Glu/NAA did not differ between the two animal groups regardless of the duration of isolation. In the subsequent partial least-squares discriminant analysis (PLS-DA), GABA/tCr and NAA/tCr were further proven to be important factors in the separation of the two animal groups. These data suggest that the neuro-metabolic imbalance between Glu and GABA levels in schizophrenic brain may be initiated with the alterations in the GABA levels.

Disclosures: **H. Heo:** None. **H.H. Lee:** None. **H. Kim:** None.

Poster

593. Schizophrenia: Circuitry Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 593.13/I29

Topic: C.15. Schizophrenia and Bi-polar Disorder

Title: Network-level dysfunction induced by perinatal phencyclidine is rescued by D-serine treatment

Authors: *S. SESHADRI[1], D. PLENZ[2];
[1]NIMH, Bethesda, MD; [2]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Cognitive dysfunction in schizophrenia (SZ) is thought to arise from disturbances in cortical network functioning, such as impaired local and long-range synchrony. However, these disturbances have not been well characterized at the neuronal level. Here, we used *in vivo* 2-photon imaging of a genetically encoded Ca2+ indicator to record spontaneous spiking activity in local populations of layer 2/3 pyramidal neurons in a rodent model of SZ. Sprague-Dawley rats were treated with phencyclidine (PCP, 10 mg/kg s.c.), an N-methyl D-aspartate (NMDA) receptor antagonist, at postnatal days 7, 9, and 11. This model recapitulates several SZ-associated phenotypes, including reduced density of fast-spiking interneurons and impaired visual working memory, which we confirmed in our cohorts. To assess network-level dysfunction in our recordings, we compared activity cascade sizes between control and PCP treated rats, and found that PCP treatment caused a significant deviation from the expected scale-free, power-law distribution. Such distributions characterize networks organized at a critical point, where several aspects of cortical processing, including information capacity and dynamic

range, are optimized. This higher-order analysis was more sensitive to PCP treatment, and therefore to disrupted excitatory-inhibitory (E-I) balance, than first- or second-order measures (e.g. firing rate and pairwise cross-correlation). Furthermore, treatment with D-serine (800 mg/kg, i.p.), an NMDA receptor co-agonist, reversed this phenotype, in parallel with rescuing impaired cognitive functioning as assessed by a visual working memory test. These results have two important implications. First, that ongoing neuronal group activity at single-cell resolution shows critical dynamics and is sensitive to E-I disruption *in vivo*. Second, that the framework of criticality could characterize cortical dysfunction in schizophrenia, and potentially serve as a biomarker for diagnosis or drug screening.

Disclosures: **S. Seshadri:** None. **D. Plenz:** None.

Poster

594. Alcohol: Effects of Prenatal Exposure

Location: Hall A

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Topic: C.17. Drugs of Abuse and Addiction

Support: The Banting Research Foundation Discovery Award (CDCB)

NSERC Discovery Grant (CDCB)

Title: Developmental ethanol exposure disrupts attention performance and prefrontal neuron function in male mice

Authors: *E. L. LOUTH, W. BIGNELL, C. L. TAYLOR, C. D. BAILEY;
Dept. of Biomed. Sci., Univ. of Guelph, Guelph, ON, Canada

Abstract: Chronic prenatal exposure to ethanol can produce a variety of teratogenic effects known collectively in humans as Fetal Alcohol Spectrum Disorder (FASD). Although deficits in attention rank among the most common and persistent neurobehavioural components of FASD, mechanisms underlying this outcome are not known. The objective of this study was to determine effects of developmental ethanol exposure on attention behaviour and on prefrontal neuron function in adult male C57BL/6 mice. Mice were exposed to either ethanol (treatment) or sucrose (control) via oral gavage during the mouse equivalent of the human second and third trimesters. We first measured attention performance using the five-choice serial reaction time test. In these experiments, adult mice from the developmental ethanol treatment group performed with lower accuracy during initial training sessions and then exhibited a greater rate of omissions

under challenging training conditions when the light stimulus was presented for short time periods. Whole-cell electrophysiological recording of pyramidal neurons located within layer VI of the medial prefrontal cortex of these same mice found decreased intrinsic excitability and increased responses to excitatory neurotransmission in mice from the developmental ethanol treatment group. Comparison of behaviour and neuron physiology identified significant correlations between attention performance and nicotinic acetylcholine receptor function in layer VI neurons of control mice, which were not present for mice that had been exposed to ethanol during development. These findings suggest that the role of prefrontal nicotinic signaling to support attention behaviour may be disrupted following developmental ethanol exposure.

Disclosures: **E.L. Louth:** None. **W. Bignell:** None. **C.L. Taylor:** None. **C.D. Bailey:** None.

Poster

594. Alcohol: Effects of Prenatal Exposure

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Program#/Poster#: 594.02/I31

Topic: C.17. Drugs of Abuse and Addiction

Title: The impact of prenatal ethanol exposure on fear memory recall and behavioral development in adulthood

Authors: *O. O. KOZANIAN, E. KORZUS, K. J. HUFFMAN;
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Abstract: *In utero* ethanol exposure produces developmental abnormalities in brain and behavior that often persist into adulthood. Fetal alcohol spectrum disorders (FASD) is an umbrella term used to describe a wide range of adverse developmental conditions caused by alcohol exposure during gestation. Children diagnosed with FASD suffer a wide range of phenotypes including growth retardation, facial dysmorphology, central nervous system anomalies and abnormal behavior and cognition. Previous research in mice suggests that abnormal cortical gene expression and circuitry may underlie reported disabilities of learning, memory, and behavior resulting from early exposure to alcohol (El Shawa et al., 2013). To further characterize behavioral deficits resulting from prenatal ethanol exposure (PrEE) in our mouse model of FASD, we conducted a series of studies to determine if behavioral deficits in sensory-motor integration and anxiety levels persist into adulthood on postnatal day (P) 50, and to evaluate the implications of PrEE on contextual fear memory recall in P50 and P70 mice. In the first study, the behavior of ethanol-exposed offspring was compared to control mice in early adulthood, extending our previous study in pre-adolescent mice (P20, El Shawa et al., 2013).

Results in P50 PrEE mice demonstrated long-term behavioral alternations that mirrored observations made previously in P20. Specifically, P50 mice performed poorly on behavioral tasks measuring sensori-motor integration and had increased anxiety compared to controls. In the second study, fear memory in PrEE mice was assessed at P50 and P70. PrEE significantly alters learning and memory of aversive stimuli at both time points in adulthood. Specially, PrEE mice showed significantly poorer performance on the fear memory recall task when compared to controls. Insight from this study will help provide new information on long-term behavioral effects of prenatal ethanol exposure and how learning and memory is impacted in people diagnosed with FASD.

Disclosures: O.O. Kozanian: None. **E. Korzus:** None. **K.J. Huffman:** None.

Poster

594. Alcohol: Effects of Prenatal Exposure

Location: Hall A

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant 1K22AA020303-0

NIH Grant P20-AA017068

Title: Delayed orbital frontal cortex recruitment allows for dorsal striatum to drive behavioral inflexibility in prenatal alcohol exposed mice

Authors: *K. L. MARQUARDT[1], J. CAVANAGH[2], K. CALDWELL[1], J. BRIGMAN[1]; [1]Neurosciences, BMSB 145, [2]Psychology, Univ. of New Mexico, Albuquerque, NM

Abstract: With a prevalence rate of 2-5% Fetal Alcohol Spectrum Disorders (FASD) are a leading cause of developmental disability in the US despite that prenatal alcohol exposure (PAE) is completely preventable. The social, learning and executive function deficits associated with PAE endure across the lifespan, preventing these individuals from thriving in a dynamic environment. FASD also has a high societal cost with estimates that as many as 46% of adolescents with FASD end up incarcerated and 29% end up being treated for alcohol and drug abuse by the age of 21. The inability of adolescents with FASD to alter their actions appropriately leads to repetitive maladaptive behaviors that can result in arrest, incarceration and substance use disorders. We have previously demonstrated that mice exposed prenatally to a clinically relevant (daily maternal BAC ~85 mg/dL) level of alcohol, during gestation, have

impaired behavioral flexibility, demonstrated by repetitive non-rewarded responses on a touch screen discrimination-reversal task. Targeted lesion, inactivation and immediate early gene expression studies have demonstrated that optimal performance of discrimination learning requires the dorsal striatum (dS) for formation of stimuli-reward associations, while the orbital frontal cortex (OFC) is critical for reward-updating during reversal. Here we integrated the well-established 'drinking in the dark' exposure model with *in vivo* electrophysiological recording during discrimination-reversal performance. Our results of single unit recordings in PAE mice suggest a delay of lateral OFC event-dependent recruitment during choice behavior in reversal and a concomitant over activation in the dS. Analysis of local field potential oscillations revealed differences in timing and power of dS and OFC low-frequencies in PAE animals during reward delivery or omission following correct and incorrect choices, respectively. These data suggest that in the FASD model, the OFC fails to properly update alterations in expected outcomes and exert regulatory control over dS activity during reversal. Ongoing studies are using dual region *in vivo* electrophysiology to analyze functional connectivity between OFC and dS to further elucidate circuitry dynamics between the two regions. The overall goal of these projects is to understand how dS over activation, due to improper recruitment of the OFC is driving behavioral inflexibility after PAE, and how these alterations may be prevented or reversed.

Disclosures: K.L. Marquardt: None. **J. Cavanagh:** None. **K. Caldwell:** None. **J. Brigman:** None.

Poster

594. Alcohol: Effects of Prenatal Exposure

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIAAA AA020051 to GC

NIAAA AA015407 to JL

Title: Consequences of prenatal drinking in the dark (DID) and neonatal ethanol intubation on spatial learning and memory in mice

Authors: A. HAWKEY[1], W. XU[2], H. LI[2], L. FIELDS[1], M. CARTER[1], J. LUO[2], G. CHEN[2], *S. BARRON[1];
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Abstract: Fetal ethanol (ETOH) exposure is associated with a variety of behavioral and learning deficits. These effects are observed in both children with Fetal Alcohol Spectrum Disorders and a variety of animal models. The data presented here represents a new exposure model using C57BL/6J mice who are unique in that they will voluntarily drink ETOH when provided limited access during their dark cycle (referred to as "Drinking in the Dark" (DID)). Previous research has examined DID as a model of fetal ETOH exposure (Boehm et al., 2008) however, this work did not include ETOH exposure during the "3rd trimester" brain growth spurt which occurs after birth in mice nor did it examine spatial learning. The hippocampus undergoes considerable perinatal development and is particularly sensitive to ETOH induced teratogenesis. Therefore, the current study used the maternal DID model and a novel, combined pre/post-natal exposure to assess whether maternal DID produces long-term effects on spatial learning and whether adding "3rd trimester exposure" exacerbates these effects. For two weeks prior to breeding and throughout pregnancy, female mice were given access to a 20% ETOH solution daily for 4 hours during their dark cycle. After birth, a subset of ETOH-exposed pups received intubations (3g/kg ETOH, 2x day) on PND 4-10. Non-treated controls were also included. Offspring (PND 35-45) were tested daily to find a hidden platform in a fixed location for 4 trials/day for 4 days using a standard Morris Water Maze. Following acquisition, a probe trial and reversal learning was examined. ETOH-treated males (both prenatal and the combined pre and postnatal ETOH group) displayed deficits in acquisition of the task. Similarly the ETOH-treated females from both groups also displayed acquisition deficits although they eventually reached performance levels similar to controls. ETOH-exposed males also performed more poorly on the probe trial and reversal learning. There were no deficits observed when tested with a visible platform. These data suggest that there may be sex differences in sensitivity to perinatal ETOH exposure on performance in the Morris water maze in C57BL/6J mice. Furthermore, the DID model which uses voluntary consumption is a useful tool to study the consequences of prenatal ETOH exposure on spatial learning.

Disclosures: **A. Hawkey:** None. **W. Xu:** None. **H. Li:** None. **L. Fields:** None. **M. Carter:** None. **J. Luo:** None. **G. Chen:** None. **S. Barron:** None.

Poster

594. Alcohol: Effects of Prenatal Exposure

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Topic: C.17. Drugs of Abuse and Addiction

Support: COBRE 1P20GM103653-01A1

Title: Moderate *in utero* alcohol exposure results in sex-dependent inflammation in the developing rat brain

Authors: *L. S. TERASAKI, J. M. SCHWARZ;
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Abstract: Activation of the developing immune system can lead to changes in neural development and long-term neural function. Recent studies show alcohol can activate the immune system; however, the fetal neuroimmune response and long-term effects of *in utero* alcohol exposure are unknown. This project aimed to determine how prenatal alcohol exposure affects the fetal brain and long-term immune and cognitive function. Pregnant Sprague-Dawley rats were left undisturbed or gavaged with either water or 50% ethanol, twice daily on embryonic (E) days 10-16. This low dose of alcohol resulted in an approximate 0.08% blood alcohol concentration for 8 hours. Real-time PCR was used to analyze pro-inflammatory cytokines and chemokines in E17 pup brains. We found that alcohol exposure increased expression of TNF-alpha, TNF-SF13, and TNF-SF13B in the hippocampus-cortex of females, while alcohol-exposed males exhibited decreased expression of CCL2 and CCL20 chemokines in the hippocampus-cortex. Additionally, maternal serum samples were analyzed for cytokine and chemokine levels, but we found no significant changes based on treatment, indicating that this level of alcohol exposure did not have a significant effect in the peripheral immune response of the mother. In a second experiment, using the same paradigm, pups were raised to adulthood to examine long-term learning and immune function. Learning was assessed using a novel object recognition task (NOR) and context pre-exposure facilitation effect (CPFE). We found that alcohol-exposed males exhibited learning deficits in NOR following a second-immune challenge with lipopolysaccharide (LPS) immediately after pre-exposure to the objects. Additionally, alcohol-exposed males exhibited a stronger neuroimmune response to LPS in adulthood, which may precipitate cognitive deficits seen in the NOR. We also examined the effect of a second dose of alcohol during adulthood as a different type of neuroimmune challenge and then tested these rats' cognitive ability by using CPFE. These on-going studies will contribute to our understanding of the impact of *in utero* alcohol exposure on the developing brain and immune system.

Disclosures: L.S. Terasaki: None. **J.M. Schwarz:** None.

Poster

594. Alcohol: Effects of Prenatal Exposure

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Program#/Poster#: 594.06/I35

Topic: C.17. Drugs of Abuse and Addiction

Title: Neuroimmune consequences of postnatal ethanol exposure and the potential anti-inflammatory and pro-cognitive benefits of ibuprofen treatment

Authors: *M. J. GOODFELLOW[1], Y. SHIN[2], D. LINDQUIST[1];
[1]Psychology, [2]Neurosci., The Ohio State Univ., Columbus, OH

Abstract: Fetal alcohol spectrum disorders (FASD) describe a range of physical and/or cognitive abnormalities that can occur in people exposed to alcohol during gestation (Streissguth, 2007). The present study utilizes a FASD rat model in which pups are administered ethanol in a binge-like manner (5 g/kg/day; 5E) via intragastric intubation across postnatal days (PD) 4-9. During this human 3rd trimester-equivalent period (Bayer et al., 1993), the developing forebrain is particularly sensitive to ethanol-induced neurotoxicity (Gil-Mohapel et al., 2010), which can cause enduring alterations in NMDA receptor subunit expression and forebrain-dependent learning and memory (e.g., trace fear conditioning or TFC, a cognitively-challenging Pavlovian conditioning task) in adolescent and adult rats (Goodfellow, Abdulla, & Lindquist, Submitted; Schreiber & Hunt, 2013; Samudio-Ruiz et al., 2010). Neuroinflammation (NIF), initiated by the interaction of ethanol with toll-like receptor 4 (Alfonso-Loeches et al., 2010), is proposed to contribute to changes in forebrain structure and function seen in FASD model animals (Kane et al., 2011; Pascual et al., 2011; Tiwari & Chopra, 2012). As a first step toward linking postnatal ethanol exposure, NIF, and observed impairments in learning and memory, we employ ibuprofen (IBU)- an anti-inflammatory drug that is commonly administered to premature human infants (Ohlsson, Walia & Shah, 2015)- to assess its ability to diminish NIF and improve TFC performance in adolescent (PD32) rats. In the current study, male and female 5E, sham-intubated (SI), and unintubated control (UC) Long-Evans rats were injected (s.c.) with IBU (100 mg/kg on PD4 followed by 50 mg/kg every 24h from PD5-20) or PBS. Pre-weanlings were euthanized (PD10 or 21) and forebrain tissue (hippocampus and medial prefrontal cortex) was analyzed via qPCR for expression of inflammatory (e.g., Ptgs2, Il1b, Tnf) and NMDA receptor subunit (Grin2A, Grin2B) genes. Preliminary data suggest postnatal ethanol exposure upregulates pro-inflammatory gene expression but that IBU may have an ameliorating effect. To examine the putative cognitive benefits of IBU treatment, separate 5E, SI and UC adolescent rats will be submitted to TFC. Reduced ethanol-induced NIF is predicted to improve TFC in 5E rats, suggesting IBU may improve forebrain-dependent cognitive function following 3rd trimester-equivalent binge-like ethanol exposure.

Disclosures: M.J. Goodfellow: None. **Y. Shin:** None. **D. Lindquist:** None.

Poster

594. Alcohol: Effects of Prenatal Exposure

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Program#/Poster#: 594.07/I36

Topic: C.17. Drugs of Abuse and Addiction

Title: Transgenerational effects of perinatal ethanol exposure: alcohol and sucrose consumption in two generations

Authors: *R. LAWRENCE[1], F. HOUK[1], V. STETTER[2];
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Abstract: Fetal alcohol spectrum disorders describe the various developmental deficiencies that result from *in utero* exposure to ethanol. Animal models have been helpful in understanding the effects of ethanol on humans. Prenatal ethanol exposure results in cognitive disabilities such as impairment in language, memory, and attention. Secondary defects in social behavior, impulsivity, inappropriate sexual conduct, and substance abuse also occur. Prenatal ethanol exposure characteristically results in higher risks of ethanol preference and addiction. Rattus norvegicus was used to simulate a human equivalent three-trimester ethanol exposure model. Rats were intubated prenatally to simulate the first and second human trimesters and the first ten days after birth to simulate the third human trimester. Ethanol preference across multiple generations was examined by using a two bottle choice test with solutions of ethanol and sucrose and sucrose. Ethanol exposure resulted in increased consumption of ethanol compared to controls whereas the F2 generation was characterized by significant reductions in alcohol consumption. However, offspring of those developmentally exposed to ethanol demonstrated a significant increase in maltose-dextrin consumption. D1R expression in the nucleus accumbens was also determined. This suggests an alteration in nucleus accumbens activity and rewarding aspects of ethanol following developmental exposure.

Disclosures: R. Lawrence: None. **F. Houk:** None. **V. Stetter:** None.

Poster

594. Alcohol: Effects of Prenatal Exposure

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant R37AA010422

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Title: Paternal alcohol imparts stress hyporesponsivity to male offspring

Authors: G. R. ROMPALA[1], A. FINEGERSH[2], *G. E. HOMANICS[2];
[1]Ctr. for Neurosci., [2]Anesthesiol., Univ. Pittsburgh, Pittsburgh, PA

Abstract: Alcohol use disorder (AUD) is associated with dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, the endocrine system critical for mounting an appropriate physiological response to stress. Adult men with a family history of alcohol abuse exhibit reduced HPA axis responsivity. Numerous studies have demonstrated that ancestral perturbations including exposure to stress or ethanol (EtOH) can impact subsequent generations via epigenetic mechanisms. In the present study, we tested the hypothesis that chronic paternal preconception EtOH exposure alters acute stress responsivity and stress-evoked EtOH drinking behaviors in offspring. Adult male mice were exposed to five weeks of intermittent vapor EtOH or control conditions and then mated with EtOH-naïve females to produce EtOH-sired (E-sired) and control-sired (C-sired) offspring. Paternal EtOH blunted corticosterone (CORT) responses to acute restraint stress selectively in male offspring. To assess stress-evoked EtOH drinking, adult E-sired and C-sired male offspring were exposed to chronic variable stress (CVS) (comprised of three days each of social defeat, forced swim, predator odor, and restraint stress exposures) over four weeks. Throughout the CVS period, mice were assessed for two-bottle choice EtOH (8% w/vol) drinking in the home cage. While we did not detect an effect of stress on EtOH consumption, C-sired males exhibited increased total fluid intake from baseline during CVS (polydipsia). In contrast, E-sired males were resistant to this stress-induced phenotype. Following CVS and 72 hours after cessation of EtOH availability in the home cage, mice were sacrificed for brain tissue collection and analysis of stress-responsive gene expression [i.e., corticotropin-releasing factor (CRF), glucocorticoid receptor (GR), and arginine vasopressin (AVP)] in the paraventricular nucleus (PVN) using rt-qPCR. CRF mRNA expression in the PVN was significantly reduced for E-sired vs C-sired males with no difference in AVP or GR expression. In addition, using bisulfite-treated DNA from the PVN and melt curve analysis, we detected significantly increased DNA methylation of the CRF promoter in E-sired vs C-sired male offspring. Levels of DNA methylation showed a significant inverse correlation with CRF gene expression. All together, we present endocrine, behavioral, molecular, and epigenetic findings suggesting that E-sired males are hyporesponsive to stress.

Disclosures: G.R. Rompala: None. **A. Finegersh:** None. **G.E. Homanics:** None.

Poster

594. Alcohol: Effects of Prenatal Exposure

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Program#/Poster#: 594.09/I38

Topic: C.17. Drugs of Abuse and Addiction

Title: The effect of early alcohol exposure on the brain and behavior in a third trimester equivalent animal model of fetal alcohol spectrum disorders

Authors: *P. C. SWART;
Human Biol., Univ. of Cape Town, Observatory, South Africa

Abstract: Introduction: Early alcohol exposure-induced changes in locomotor activity, learning and memory, neurotransmission and proteins were measured using an animal model of fetal alcohol spectrum disorders (FASD). It was also investigated whether a memory enhancing drug (Vinpocetine) could alleviate early alcohol exposure-induced changes. Hence providing insight towards the mechanisms behind FASD. Methods: A third trimester equivalent animal model of FASD was used in which Sprague-Dawley rats were administered 12 % ethanol (EtOH) solution (4 g/kg/day i.p.) or saline volume control from P4 to P9. From P25 to P31, randomly selected male rats were treated with Vinpocetine (Vinp) (20 g/kg/day i.p.) or DMSO vehicle control (saline+DMSO-; EtOH+DMSO- and EtOH+Vinp-treated rats) prior to undergoing behavioural testing in the Open Field and Morris Water Maze (MWM). All rats were decapitated on P31, after which the prefrontal cortex (PFC), dorsal hippocampus (DH) and striatum were removed. The striatum of untreated rats were used in an *in vitro* superfusion experiment to asses glutamatergic receptor and dopaminergic functioning using radioactively labelled [3H] Dopamine (DA). The rest of the dissected tissue from treated rats was stored in liquid nitrogen for later use in a BDNF ELISA, Western Blot and proteomic analysis. Results: Behavioural results show that EtOH+Vinp-treated rats learnt better during the acquisition trials of the MWM compared to EtOH+DMSO-treated rats on days 1, 2 and 4. However, during the probe trial no significant difference was observed in the time spent in the platform quadrant between experimental groups. Results from *in vitro* superfusion experiments showed no differences in [3H]DA release between saline- and EtOH-treated rats. BDNF was significantly decreased in the PFC of EtOH+Vinp-treated rats. MKP-1 was significantly increased in the PFC of EtOH+Vinp-treated rats. P-ERK was significantly decreased in the PFC and significantly increased in the DH of EtOH+DMSO-treated rats. An increase in P-GSK was observed in the DH of EtOH+Vinp-treated rats. Similarly, synaptophysin was increased in the DH of EtOH+Vinp-treated rats. Conclusion: EtOH induced learning deficits in the MWM during acquisition trials however, all animals were able to re-call the location of the platform during the probe trial. This indicates differential learning between groups however memory remains unaffected. EtOH did not affect glutamatergic receptor or dopaminergic function. Therefore, the behavioural results may be explained by differential protein expression between experimental groups in the PFC and DH.

Disclosures: **P.C. Swart:** A. Employment/Salary (full or part-time):; University of Cape Town.

Poster

594. Alcohol: Effects of Prenatal Exposure

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Topic: C.17. Drugs of Abuse and Addiction

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P20AA017068-03S1

1P50AA022534-01

Title: Magnetoencephalography study on multisensory integration in adolescents with fetal alcohol spectrum disorder

Authors: *A. D. BOLANOS[1,4], B. A. COFFMAN[4,5], J. F. L. PINNER[2], P. KODITUWAKKU[3], J. M. STEPHEN[4];
[2]Psychology, [3]Pediatrics, [1]Univ. of New Mexico, Albuquerque, NM; [4]The Mind Res. Network, Albuquerque, NM; [5]Psychiatry, Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA

Abstract: It is now known that children exposed to alcohol *in utero* display a broad range of cognitive and behavioral deficits along with functional and structural neural anomalies. Children with fetal alcohol spectrum disorder (FASD) have impairments in sensory processing and executive functioning, suggesting atypical brain development. Here we measure brain responses using magnetoencephalography (MEG) during passive auditory (A - left and right monaural 1000 Hz tone), somatosensory (S- air puff stimulus to left and right index finger), and multisensory (synchronous auditory/somatosensory) stimulation from 19 adolescents with FASD and 23 age-matched, typically developing controls. A cross-hemisphere multisensory paradigm (left A/left S, LA/RS, RA/RS and RA/LS) was employed to assess hemispheric connectivity deficits in children with FASD. Based on the role of neural oscillations in multisensory integration, we hypothesized that neural oscillations would be altered in adolescents with FASD. Time-frequency analysis of the MEG data revealed a significant decrease in oscillatory power for six (LS, RS, RA/RS, RA/LS, LA/RS, and LA/LS) out of the eight conditions in the FASD group based on permutation testing of significant group differences. Gamma power was reduced in two multisensory conditions (RA/RS and RA/LS) in the FASD group relative to controls.

Also, an increase in beta and gamma band power was noted in the FASD group compared to the control group, for multisensory conditions associated with left auditory stimulation (LA/RS and LA/LS). Through one-sample t-tests corrected for multiple comparisons, we noted that between-group differences in multisensory conditions were accompanied by a significant within-group increase in oscillatory power relative to baseline in the control group and a decrease in the FASD group. Furthermore, results revealed that unisensory oscillatory power predicted multisensory oscillatory power more strongly in the control group than in the FASD group. Yet, oscillatory power only correlated with attention and impulsivity scores in the FASD group. The present results provide further evidence of abnormal gamma band oscillations in adolescents with FASD when responding to sensory stimuli. Differential response to left vs. right auditory stimuli may indicate hemispheric differences in neural activity related to prenatal alcohol exposure. These alterations in neural oscillations may contribute to the neurobehavioral deficits experienced by individuals with FASD by restricting their ability to respond properly to external stimuli during day-to-day interactions.

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Poster

594. Alcohol: Effects of Prenatal Exposure

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant AA019462

Title: Female rats exposed to moderate levels of ethanol during gestation display modified spatial navigation behavior

Authors: *C. M. MAGCALAS[1], D. BARTO[2], C. W. BIRD[2], S. DAVIES[3], D. D. SAVAGE[3], D. A. HAMILTON[4];
[2]Psychology, [3]Neurosciences, [4]Psychology and Neurosciences, [1]Univ. of New Mexico, Albuquerque, NM

Abstract: Prenatal alcohol exposure (PAE) is associated with structural and physiological changes that impact the central nervous system and can result in persistent negative consequences in a broad spectrum of cognitive and behavioral domains including deficits in motor behavior, social behavior, and behavioral flexibility. Previous studies have characterized

the influence of PAE on spatial navigation and behavioral flexibility through various behavioral paradigms including the Morris water task (MWT). The current study focuses on examining the behavioral consequences of PAE on directional and place navigation through the use of the MWT. Pregnant rat dams voluntarily consumed saccharin (SAC) water containing 0% or 5% ethanol (EtOH) for 4 hours per day during the entire gestational period. The pups matured and 16 adult males and 16 adult females were tested in a variant of the MWT. In order to assess directional and place navigation the animals were tested in a 2-day hidden platform protocol and a 2-day cued platform protocol with a 2 week time period between sessions. Day 1 of the hidden protocol consisted of 12 training trials and 1 pool shift test. Day 2 consisted of 8 training trials, 1 pool shift test (opposite of the first test), 4 training trials, and 1 probe trial. The pool shift test consisted of moving the pool to a secondary position. The platform either moves with the pool to a relative location in the pool (directional navigation) or stays in the absolute location in the room (place navigation). Following a 2-week period the rats were tested in a cued variant of the MWT. The cued variant followed the same scheme as the hidden variant except that there were 8 preferred reversal trials added to the end of day 2. The reversal paradigm involved shifting the pool while the platform was placed in the opposite of the location that the animal showed preference to. There were no significant differences between PAE treatment or sexes in the hidden or cued training trials. In the hidden variant there was a significant interaction in the females between preference for the absolute or relative location and PAE. The SAC female rats displayed a preference for the relative platform location, which is consistent with previous findings, while EtOH female rats displayed a preference for the absolute location. These outcomes suggest that animals may have distinct search patterns that may be sex specific and can be influenced by PAE. [Supported by grant AA019462 to DH].

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Poster

594. Alcohol: Effects of Prenatal Exposure

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NIH 1 RO1 DA027487

Beckman Postdoctoral Fellowship Award

Title: Impact of postnatal 5-7-9 alcohol exposure and voluntary exercise on prefrontal plasticity and behavior

Authors: *G. F. HAMILTON, I. J. HERNANDEZ, C. P. KREBS, J. S. RHODES;
Univ. of Ilinois Urbana-Champaign, Champaign, IL

Abstract: Developmental alcohol exposure in humans can result in a wide range of deficits collectively referred to as Fetal Alcohol Spectrum Disorders (FASD). FASD-related impairments in cognition and learning persist into adulthood and are accompanied by structural changes in the prefrontal cortex (PFC). In animal models of FASD, neonatal alcohol exposure significantly altered medial PFC (mPFC) pyramidal neuron dendritic morphology. Basilar dendrites of mPFC neurons receive indirect connections from the mediodorsal nucleus of the thalamus via parvalbumin+ GABAergic interneurons. Therefore, in this experiment we examined the impact of a postnatal (PD) 5, 7 and 9 alcohol exposure on 1) the number of mPFC parvalbumin+ GABAergic interneurons and 2) behavioral performance on both the Rotarod and the Passive Avoidance tasks. Further, we explored the therapeutic role of aerobic exercise. Exercise consistently has been shown to improve hippocampal function and plasticity in the alcohol exposed brain, while its influence on the mPFC is much less established. In this experiment, animals received a treatment of either saline or a 20% ethanol solution at 5 g/kg split into two doses, two hours apart on postnatal day (PD) 5, 7, and 9. Animals were weaned on PD 23 and, beginning on PD 35, all animals received either a running or sedentary intervention for 48 days. Animals were perfused on PD 83 and the number of mPFC parvalbumin+ interneurons was measured. Preliminary data suggest that a PD 5, 7 and 9 alcohol exposure reduces the number of parvalbumin+ cells in the mPFC. The role of exercise on the number of parvalbumin+ interneurons is currently being determined. Neonatal alcohol exposure significantly impaired acquisition of the Passive Avoidance task, regardless of exercise intervention. On Day 2, exercise significantly increased retention of the Passive Avoidance task, regardless of postnatal condition. All runners remained on the rotarod significantly longer than did all sedentary animals. Overall, these data examine the long-term, possibly detrimental, influence of neonatal alcohol exposure and the potentially beneficial impact of voluntary exercise in the alcohol-exposed brain.

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Poster

594. Alcohol: Effects of Prenatal Exposure

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Support: NIH Grant AA019462

NIH Grant AA019884

Title: Reduced agonistic behavior in male rats exposed to ethanol prenatally following blockade of GluN2B containing NMDA receptors in agranular insular cortex

Authors: *C. W. BIRD[1], D. BARTO[1], C. MAGCALAS[1], C. I. RODRIGUEZ[1], T. DONALDSON[1], S. DAVIES[2], D. D. SAVAGE[2], D. A. HAMILTON[1,2];
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Abstract: Moderate exposure to alcohol during development leads to subtle neurobiolgical effects, which are diagnosed under the umbrella term fetal alcohol spectrum disorders (FASDs). Alterations in social behaviors are a frequently observed negative consequence of maternal drinking, as children with FASDs display inappropriate aggressive behaviors, have altered responses to social cues, and increased prevalence of conduct disorder. Rodent models of FASDs mimic the behavioral alterations seen in humans, with rats exposed to ethanol during development displaying increased aggressive behaviors, decreased social investigation, and altered play behavior. Prior work from our laboratory has observed increased agonistic behaviors in adult male rats following prenatal alcohol exposure (PAE), as well increased expression of GluN2B containing NMDA receptors in agranular insular cortex (AID), a frontocortical subregion specifically implicated in modulating social behaviors. This study was undertaken to determine if GluN2B antagonism has a significant effect on agonistic social behaviors in PAE rats. Using a voluntary ethanol exposure paradigm, rat dams were allowed to drink a saccharin sweetened solution of either 0% or 5% ethanol for 4 hours per day throughout gestation. Following parturition and weaning, rats from the same prenatal diet condition were pair-housed, and at 6-8 months of age were implanted with cannulae into AID. Animals were isolated for 24 hours before ifenprodil (1 μg), a GluN2B specific NMDA receptor antagonist, or vehicle was infused bilaterally into AID, and after 15 minutes they were recorded in a social interaction chamber. The following week animals were again isolated for 24 hours, then infused with the opposite drug treatment and observed again. A significant effect of ifenprodil infusion was observed on agonistic wrestling behavior in males, as PAE rats infused with vehicle displayed increased wrestling behavior compared to control rats that was normalized to controls following ifenprodil infusion. In female rats ifenprodil infusion increased agonistic wrestling behavior regardless of prenatal diet condition, mirroring previously observed sexually dimorphic effects of PAE exposure on social behaviors. Together, these data indicate that GluN2B containing NMDA receptors in AID play a role in social behavior and may underlie alterations observed in PAE animals.

Disclosures: **C.W. Bird:** None. **D. Barto:** None. **C. Magcalas:** None. **C.I. Rodriguez:** None. **T. Donaldson:** None. **S. Davies:** None. **D.D. Savage:** None. **D.A. Hamilton:** None.

Poster

594. Alcohol: Effects of Prenatal Exposure

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 594.14/I43

Topic: C.17. Drugs of Abuse and Addiction

Support: PHS NIH R01AA023410

Title: *In utero* ethanol exposure disrupts migration of glutamatergic neurons into the cortical plate

Authors: *L. C. DELATOUR, H. H. YEH;
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Abstract: Exposure to ethanol during fetal brain development is one of the leading causes of preventable, non-genetic intellectual disability. However, the mechanisms leading to the detrimental effects of *in utero* ethanol exposure on brain development are multifaceted and not fully understood. We have previously reported that exposure to ethanol *in utero* disrupts tangential migration of GABAergic cortical interneurons that occurs early in embryonic corticogenesis. Here we initiated an investigation into the effect of prenatal ethanol exposure on radial migration, involving radial glial cells (RGCs). These cells are critical not only to the development of cortical lamination and radial migration, but also to producing neurons directly as well as indirectly through intermediate progenitor cells (IPCs). During neurogenesis, the expression of transcription factors Pax6, Tbr2, and Tbr1 correspond to the progression from RGCs to IPCs, and to postmitotic glutamatergic neurons, respectively. We used a 3-day binge-drinking paradigm in which pregnant dams were exposed to ethanol (5% in liquid food) from embryonic day(E) 14.5 through E16.5, corresponding to a period of active neurogenesis and migration. In 30-µm coronal cryosections through the E16.5 embryonic telencephalon, we noted aberrant expression of both Tbr2 and Tbr1 in the ethanol-exposed cohort. In control animals, Tbr1 immunoreactivity was greatest in the cortical plate (CP). However, in the ethanol-exposed telencephalon, Tbr1 immunoreactive profiles were dispersed throughout both the CP and intermediate zone. Tbr2 expression also differed between control and ethanol-exposed animals. To investigate whether the observed changes in migration were due to a difference in neuronal proliferation, pulse-labeling experiments were conducted with BrdU, analyzed 2 hours post IP injection on E14.5. The results revealed a different pattern of migration of the BrdU+ cells prior

to entry into the cortical plate and a trend towards an increase in their overall number in the cortex of ethanol-exposed relative to control cohorts. Pyramidal neurons in the cortex are glutamatergic. The results of our immunostaining indicated that at least a subpopulation of them express Tbr1 at some point in their maturation. Our results thus far suggest that ethanol exposure *in utero* affects the radial migration of Tbr1- and Tbr2-expressing cells. Ongoing studies are examining (1) whether changes in the radial glial scaffolding could be affecting the migration of these glutamatergic neurons into the CP, and (2) the short- and long-term effects of *in utero* ethanol exposure on pyramidal cells in the cortex. *Supported by PHS NIH R01AA023410*

Disclosures: L.C. Delatour: None. **H.H. Yeh:** None.

Poster

594. Alcohol: Effects of Prenatal Exposure

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH NIAAA Grant 1P50 AA022534-01

NIH NIAAA Grant 5R01AA017449

Title: Impaired production of oligodendrocyte lineage cells in a third trimester-equivalent mouse model of fetal alcohol spectrum disorder (FASD)

Authors: J. NEWVILLE[1], C. F. VALENZUELA[1], L. LI[1], L. JANTZIE[2], *L. A. CUNNINGHAM[1];
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Abstract: Recent imaging studies have demonstrated white matter abnormalities in individuals with clinical FASD, but the underlying mechanisms are unknown. Here, we evaluated the impact of early postnatal alcohol exposure on the production of oligodendrocyte lineage cells using a third trimester equivalent preclinical mouse model of FASD, in which pups were exposed to alcohol during a critical period of rapid myelination. We utilized the Nestin-CreER^{T2}/YFP strain to distinguish between oligodendrocyte lineage cells derived from the postnatal subventricular zone (SVZ; Olig2^{+}/YFP^{+}) *vs.* those originating during embryonic development (Olig2^{+}/YFP^{-}). Nestin-CreER^{T2}/YFP pups received a single intraperitoneal injection of tamoxifen (33 mg/kg) at postnatal day 2 (P2) to label SVZ progenitors, and cages containing both mothers and pups were placed into inhalation chambers where they were exposed to ethanol vapors or air (control) for

four hours daily from P3 through P15 (3 litters/group). The mean daily pup blood alcohol concentration over the 13 days of exposure was 48 mM within a 24-84 mM range. Mice from each litter were sacrificed at P16 or P50 and the densities of $Olig2^+$ and YFP^+ cells within the septal region of the corpus callosum were quantified using immunofluorescence and confocal stereology. Although alcohol had no effect on the density of $Olig2^+/YFP^-$ cells at P16 (1547 $\pm$ 110 vs. 1335 $\pm$ 337 cells/mm^2, air vs. alcohol, n=4-5 mice/group), the density of $Olig2^+/YFP^-$ cells was significantly decreased by approximately 32% in alcohol exposed mice compared to controls at P50 (2424 $\pm$ 278 vs. 1546 $\pm$ 57 cells/mm^2, air vs. alcohol, p=0.0342, n=7-9). Interestingly, there was no effect of alcohol on the density of SVZ-derived oligodendrocyte lineage cells ($Olig2^+/YFP^+$) at either P16 or P50. SVZ-derived $Olig2^+$ cells comprised approximately 20% of the total oligodendrocyte lineage cells within the corpus callosum across all groups except the P50 alcohol exposed group (25%), due to loss of $Olig2^+/YFP^-$ cells at this age. These results indicate that third trimester equivalent alcohol exposure results in a delayed, long-term deficit in oligodendrocyte production that becomes manifest in early adulthood. Furthermore, these data suggest that the oligodendrocyte lineage cells derived from the postnatal SVZ are relatively insensitive to the effects of early postnatal alcohol exposure, but do not fully compensate for loss of non-SVZ derived cells.

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Poster

594. Alcohol: Effects of Prenatal Exposure

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Brain & Behavior Research Foundation

Brain Science Foundation

Title: Developmental alcohol exposure impairs activity-dependent S-Nitrosylation of NDEL1 for neuronal maturation

Authors: *A. SAITO[1,3], Y. TANIGUCHI[1], S.-H. KIM[1], B. SELVAKUMAR[2], M. D. BALLINGER[1], J. SABRA[1], M. JALLOW[1], P. YAN[1], K. ITO[1], S. HIROTSUNE[4], A. WYNSHAW-BORIS[5], S. H. SNYDER[2], A. SAWA[1,2], A. KAMIYA[1];
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Abstract: Maternal alcohol exposure during pregnancy is an environmental risk for disturbed brain function, causing impaired cognitive and social functioning in exposed offspring. Preclinical studies demonstrate that alcohol exposure during development effects multiple processes of brain development, though the underlying molecular mechanisms remain poorly understood. Here we present that developmental alcohol exposure impairs dendritic development via disruption of neuronal nitric oxide synthase (nNOS)-mediated *S*-Nitrosylation of nuclear distribution element-like (NDEL1). *S*-Nitrosylation of NDEL1 accelerates dendritic arborization in the cerebral cortex. This posttranslational modification is enhanced by NMDA receptor-mediated neuronal activity, a main regulator of dendritic formation. Importantly, dendritic deficits caused by alcohol exposure are rescued by up-regulation of NDEL1 *S*-Nitrosylation, suggesting that altered *S*-Nitrosylation of NDEL1 acts as a key pathological factor mediating neurodevelopmental abnormalities caused by maternal alcohol use.

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Poster

594. Alcohol: Effects of Prenatal Exposure

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Topic: C.17. Drugs of Abuse and Addiction

Support: PHS R01AA023410

Title: Bumetanide treatment mitigates ethanol-induced deficits in PFC-dependent behavior associated with interneuronopathy in a mouse model of FASD

Authors: *H. H. YEH, A. G. J. SKORPUT, V. P. GUPTA, P. W. L. YEH, J. T. WEISS, N. M. SIMINERI;
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Abstract: GABA, via GABAA receptors, regulates corticopetal migration of GABAergic cortical interneurons during corticogenesis. This GABA-mediated migration is accelerated *in vivo* by prenatal exposure to ethanol, a positive modulator of the GABAA receptor. GABAA receptor activation depolarizes these cells due to increased developmental expression of the Na+-K+-2Cl- cotransporter (NKCC1), maintaining [Cl-]i higher than [Cl-]e. We hypothesized that ethanol, in potentiating GABAA receptor function, surges chloride efflux, augmenting the GABA-induced depolarization and, thereby, boosting tangential migration. Here, we tested the corollary mechanistic hypothesis that bumetanide, an inhibitor of NKCC1 activity in the brain, mitigates the ethanol-induced aberrant tangential migration. In addition, ethanol-exposed young adult offspring exhibited enduring interneuronopathy in the medial prefrontal cortex as well as decreased behavioral flexibility. We report here on our ongoing investigations into bumetanide's ability to prevent ethanol-induced aberrant migration in the short-term and the behavioral deficit in the long-term. Nkx2.1Cre/Ai14 mice harbor tdTomato-fluorescent MGE-derived GABAergic interneurons. On E14.5, organotypic slice cultures prepared from Nkx2.1-tdTomato embryos were divided into 4 groups: Control; 50mM Ethanol; 20μM Bumetanide; 50mM Ethanol+20μM Bumetanide. Ethanol and/or bumetanide were added to the slice medium at t1hr. The slices were fixed at t25hr, and the number of tdTomato-fluorescent cells was analyzed for each group in a blinded fashion. Such analyses uncovered significantly higher numbers of tdTomato-flourescent cells in slices exposed to ethanol, as reported *in vivo*, indicating a greater degree of tangential migration into the neocortex. The number of migrating cells was near control levels in the group treated with ethanol+bumetanide, suggesting that bumetanide prevented the ethanol-induced heightened tangential migration. Cell counts were similar in slice cultures treated with and without bumetanide alone. With binge-type gestational ethanol exposure *in vivo* (5% w/w in food, E13.5-E16.5), bumetanide prevented the ethanol-induced increase in Nkx2.1+ cells. Young adult offspring treated daily with bumetanide during the period of binge-type ethanol exposure did not exhibit the increase in perseverative error upon reversal of a spatial navigation task, as was seen in ethanol-exposed offspring. These results suggest that bumetanide treatment may have therapeutic benefits in decreasing cortical dysfunction associated with interneuronopathy in the pathophysiology of FASD.

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Poster

594. Alcohol: Effects of Prenatal Exposure

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Topic: C.17. Drugs of Abuse and Addiction

Support: NSERC311637

Title: Embryonic alcohol exposure increases apoptosis in the zebrafish brain; a strain comparison

Authors: *S. MAHABIR[1], D. CHATTERJEE[2], R. GERLAI[2];
[1]Univ. of Toronto Mississauga, Mississauga, ON, Canada; [2]Psychology, Univ. of Toronto Mississauga, Toronto, ON, Canada

Abstract: Fetal alcohol spectrum disorder (FASD) is the term used to describe children that have been exposed to alcohol in the womb. Individuals that are affected display a range of severe to mild central nervous system (CNS) abnormalities. The severity of this disorder varies depending on the dose and time of exposure and genetic background of the individual. The biological mechanisms that underlie how alcohol exerts its deleterious effects in vertebrates are complex and poorly understood. The zebrafish has been a popular model for developmental biology, and recently has also started to be employed for FASD research. When exposed to low concentration of alcohol during embryonic development, zebrafish show long lasting behavioural alterations that persist in adulthood. These alternations are correlated with changes in the dopaminergic and serotonergic systems. One potential mechanism that embryonic alcohol may be acting on is programmed cell death or apoptosis. The present study investigates the effects of embryonic alcohol exposure on apoptosis and two proteins in the signaling pathway leading to apoptosis. We used 3 different zebrafish strains AB, TU and TL. Zebrafish embryos were exposed to ethanol (EtOH) at 24 hours post-fertilization (hpf) for 2 hours using three external bath concentrations, 0.00%, 0.50% or 1.00% EtOH (vol/vol%). The embryos were analyzed for apoptosis, pro and anti apoptotic proteins Bax and Bcl2 at 26 hours post-alcohol exposure. Results show that embryonic alcohol increases apoptosis in fish of the AB and TL strains but not in fish of the TU strain. Moreover, AB and TL zebrafish also show an increase in pro-apoptotic protein Bax and no change in anti-apoptotic protein Bcl2 in the alcohol-exposed group. TU strain fish, on the other hand, did not show any change in pro apoptotic and anti apoptotic proteins in response to embryonic alcohol exposure. We conclude that apoptosis induced by embryonic alcohol exposure is mediated by Bax and Bcl2 proteins and that characterization of zebrafish strains may allow one to discover potential protective mechanisms. Given the translational

relevance of the zebrafish, our studies may help us further understand the biological mechanisms underlying FASD in humans.

Disclosures: **S. Mahabir:** None. **D. Chatterjee:** None. **R. Gerlai:** None.

Poster

594. Alcohol: Effects of Prenatal Exposure

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH Grant R37-AA015614

Title: Third trimester-equivalent ethanol exposure causes micro-bleeds in the rat cerebral cortex

Authors: J. WELCH, J. MAYFIELD, *C. F. VALENZUELA;
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Abstract: Exposure to ethanol during fetal development causes a wide range of alterations in many organs and systems, including the brain. It is known that ethanol exposure results in a number of molecular pathologies; however, experimental evidence also suggests that ethanol can indirectly affect brain development by altering maternal and fetal vascular development. Spontaneous hemorrhage has been documented in the cerebral cortex of developing rats, suggesting that immature cortical capillaries are susceptible to rupture (Pavlik and Mares, *Neuroscience Letters*. 141 (1992) 177-180). In this study, we examined whether ethanol exposure during the rat equivalent to the 3rd trimester of human pregnancy causes bleeding in the developing brain. Pregnant Sprague-Dawley dams were exposed with their pups to air or ethanol on postnatal days 3, 4, and 5 from 10 am-1 pm daily using vapor inhalation chambers. This paradigm results in peak ethanol levels near 75 mM in the pup serum. Brains were examined at postnatal day 6 and, as expected, demonstrated spontaneous micro-bleeds in the surface of the cerebral cortex of air exposed control pups (1.6 ± 0.08 bleeds/brain; n = 4). In brains from ethanol exposed pups, the number of bleeds per brain was significantly increased to 23 ± 0.08 (n = 7; p = 0.006 by Mann-Whitney test). Coronal brain sections were examined and subsequent regional analysis revealed that the vast majority of the micro-bleeds were located in the cerebral cortex. Experiments are currently underway to determine the age- and dose-dependency of this effect. Our results suggest that heavy ethanol exposure during the 3rd trimester equivalent can weaken the capillary vasculature in the developing cerebral cortex, causing micro-hemorrhages

in this brain region. We conclude that this effect could be one of the mechanisms underlying the behavioral deficits associated with fetal alcohol spectrum disorders.

Disclosures: **J. Welch:** None. **J. Mayfield:** None. **C.F. Valenzuela:** None.

Poster

594. Alcohol: Effects of Prenatal Exposure

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Topic: C.17. Drugs of Abuse and Addiction

Support: NIH AA017978

Title: *Ex vivo* model of prenatal alcohol exposure: development and confirmation of validity

Authors: ***E. TUNC-OZCAN**[1], A. B. FERREIRA[2], E. E. REDEI[1];
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Abstract: Fetal Alcohol Spectrum Disorder (FASD) encompasses a continuum of disabilities caused by prenatal alcohol exposure (PE). Hippocampus-based cognitive deficits are among the most debilitating consequences of PE and insulin pathway genes are known to be involved in regulating learning and memory processes in the hippocampus. Currently, no treatment is available for FASD. Development and screening of novel drug targets often relies on *in vitro* studies, which are scarce in FASD research. For this reason, we developed an *ex vivo* model and compared transcript levels of insulin pathway genes between the *ex vivo* primary hippocampal culture and embryonic day 21 (E21) hippocampi. Using our established animal model of FASD, pregnant rats were fed control and ethanol-containing diets from gestational day 8 to 20. Male and female E21 hippocampi were dissected, and male and female E18 hippocampi were cultured together, or separately, for three days (days *in vitro* 3 - DIV3) using standard primary hippocampal culturing techniques. Transcript levels of insulin-like growth factor 2 (Igf2), Igf2 receptor (Igf2r), insulin receptor (Insr), ras-guanine nucleotide releasing factor 1 (Rasgrf1), growth factor receptor-bound protein 10 (Grb10) and pleomorphic adenoma gene-like 1 (Plagl1/Zac1) were measured by quantitative RT-PCR in the fetal hippocampi and from the *ex vivo* primary hippocampal culture in all prenatal treatment groups. When male and female hippocampi were combined by litter, primary hippocampal neurons at DIV3 showed a co-expression pattern of the above genes that was very similar to those obtained from the E21 hippocampus. Furthermore, transcript levels of these genes were affected by PE similarly in the E21 hippocampi compared to the primary hippocampal cultures at DIV3. When male and female

hippocampi from the same litter were handled separately, sex differences in gene expression observed in the fetal hippocampus at E21 were not present in the *ex vivo* model, with the exception of Grb10. PE-induced expression differences were also seen between the female E21 and the cultured hippocampi for Igf2, Rasgrf1 and Zac1. These sex differences are likely due to the developmental events between E18 and E21, and the known size differences between the male and female fetal hippocampus, which is eliminated in the culture. Taken together, primary hippocampal culture could be useful to develop and characterize drug-based interventions to reverse PE-induced hippocampal dysregulation.

Disclosures: E. Tunc-ozcan: None. **A.B. Ferreira:** None. **E.E. Redei:** None.

Poster

594. Alcohol: Effects of Prenatal Exposure

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Topic: C.17. Drugs of Abuse and Addiction

Support: Natural Sciences and Engineering Research Council of Canada (NSERC Discovery Grant 372405-2009)

Health Sciences Center Foundation (HSCF)

Title: DNA methylation, neural stem cells and Fetal Alcohol Spectrum Disorders; implicating the role of MeCP2 regulatory network

Authors: *M. RASTEGAR, V. R. B. LIYANAGE, R. M. ZACHARIAH;
Biochem. and Med. Genet., Univ. of Manitoba, Winnipeg, MB, Canada

Abstract: Fetal alcohol spectrum disorders (FASD) are intellectual disabilities with facial-growth abnormalities and compromised brain function due to maternal alcohol exposure. FASD are common neurodevelopmental disorders that affect 1-3% of live-born children. Currently, FASD has no cure and the molecular mechanisms by which alcohol deregulates the gene expression program of differentiating neurons are poorly understood. Characterizing the cellular and molecular deficiencies of the affected neurons and identifying clinically relevant drugs to rescue these neurons are the major focus of this study. FASD etiology is thought to be *via* alcohol-gene interactions in differentiating embryonic neural stem cells during brain development. This process is tightly regulated by epigenetic mechanisms and epigenetic factors. One of the best-studied epigenetic mechanisms that control brain development is DNA

methylation. The main protein that binds to the methylated DNA in brain is MeCP2 with key roles in brain development and function, recently linked to FASD. Accordingly, altered MeCP2 levels or loss-of-function mutations cause Rett Syndrome, autism, and X-linked mental retardation. Our initial studies in MeCP2-deficient mouse were proof-of-principle for the role of MeCP2 isoforms in neuronal maturation. We reported the developmental and cell type-specific expression of *Mecp2/*MeCP2 isoforms in brain. We identified and characterized *Mecp2* regulatory elements that are controlled by DNA methylation. We now show that these sequences are involved in *Mecp2*/MeCP2 deregulation by ethanol, associated with altered inactive (5mC: 5-methylcytosine) and active (5hmC: 5-hydroxymethylcytosine) DNA marks. We find that different modes of ethanol exposure [continuous, single time exposure, or withdrawal] either induce or decrease *Mecp2*/MeCP2. In response to ethanol, we show globally altered 5mC and 5hmC levels associated with increased neuronal neurite branching that might be biologically important. MeCP2 is the main 5mC- and 5hmC- binding protein in brain and we show selective deregulation of MeCP2 regulatory network by ethanol. Further, we show altered *Mecp2/*MeCP2 levels by an epigenetic drug (DNA methylation inhibitor) that may have future applications for MeCP2-associated neurodevelopmental disorders. DNA methylation is reversible, thus uncovering deregulation of MeCP2 regulatory network and DNA methylation-mediated effects of ethanol in neurons is critical for possible drug therapy strategies. Our results indicate that targeting MeCP2 network might be a possible intervention-therapeutic avenue to rescue impaired neuronal function caused by ethanol.

Disclosures: M. Rastegar: None. **V.R.B. Liyanage:** None. **R.M. Zachariah:** None.

Poster

594. Alcohol: Effects of Prenatal Exposure

Location: Hall A

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Program#/Poster#: 594.22/J3

Topic: C.17. Drugs of Abuse and Addiction

Title: Gene expression profiling and genome-wide sequencing of methylated DNA identified dynamic changes in the methylome during early development

Authors: C. MANDAL[1], K. JUNG[2], S. KIM[2], K. PARK[2], J. CHAI[2], Y. LEE[2], *Y.-G. CHAI[3]; [1]Hanyang university, Ansan, Korea, Republic of; [3]Mol. Biol. & Life Sci., [2]Hanyang Univ., Ansan, Korea, Republic of

Abstract: Alcohol (ethanol, EtOH) consumption during pregnancy causes a variety of prenatal and postnatal disorders collectively referred to as fetal alcohol spectrum disorders (FASDs).

Recently, increasing evidence indicates that alcohol may induce epigenetic alterations, in particular aberrant DNA methylation patterns. To better understand the molecular events leading to FASDs, we performed a genome-wide transcriptomic (mRNA-seq) and DNA-methylom analysis (MBD-seq) of ethanol exposed emryoid bodies. Combined transcriptomic and DNA methylomic analysis produced a list of differentiation-related genes dysregulated by ethanol-induced DNA methylation changes. We also short listed 19 transcription factor encoding genes which are regulated through DNA methylation. These findings should help in deciphering the precise mechanisms of alcohol-induced teratogenesis.

Disclosures: C. Mandal: None. **K. Jung:** None. **S. Kim:** None. **K. Park:** None. **J. Chai:** None. **Y. Lee:** None. **Y. Chai:** None.

Poster

595. Drug Delivery

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Topic: C.19. Drug Discovery and Development

Support: DA032837

DA026582

Title: The importance of the 6- and 7-positions of tetrahydroisoquinolines as selective antagonists for the orexin 1 receptor

Authors: *Y. ZHANG[1], D. A. PERREY[1], A. M. DECKER[1], J.-X. LI[2], B. P. GILMOUR[1], B. F. THOMAS[1], D. L. HARRIS[1], S. P. RUNYON[1];
[1]Res. Triangle Inst., Research Triangle Park, NC; [2]Univ. at Buffalo, Buffalo, NY

Abstract: Selective antagonism of the orexin 1 (OX1) receptor has been proposed as a potential mechanism for treatment of drug addiction. We have previously studied the structure-activity relationships of tetrahydroisoquinoline-based antagonists which normally have di-substitutions at the 6- and 7-positions. Here we aim to elucidate the respective role of 6- and 7-substitution by preparation of a series of either 6-substituted tetrahydroisoquinolines (with no 7-substituents) or vice versa. These compounds were characterized by MS, NMR and HPLC, and then evaluated in calcium-dependent functional assays in RD-HGA16 (Molecular Devices) cell lines stably expressing either the OX1 or OX2 receptor. We found that 7-substituted tetrahydroisoquinolines showed potent antagonism of OX1, with several compounds having Ke values of low nM,

whereas the 6-substituted analogs generally showed modest potency. These results suggest that the 7-position is more important for OX1 antagonism. Several compounds demonstrated insurmountable antagonism at the OX1 receptor and studies on incubation time suggest that these compounds are competitive antagonists with slow dissociation rates. These results will facilitate the development of potent and selective OX1 antagonists as medications for the treatment of drug addiction and related conditions.

Disclosures: **Y. Zhang:** None. **D.A. Perrey:** None. **A.M. Decker:** None. **J. Li:** None. **B.P. Gilmour:** None. **B.F. Thomas:** None. **D.L. Harris:** None. **S.P. Runyon:** None.

Poster

595. Drug Delivery

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Program#/Poster#: 595.02/J5

Topic: C.19. Drug Discovery and Development

Title: Feasibility of targeted intracerebral administration in the cynomolgus monkey

Authors: ***J. DOUVILLE**, F. EMOND, C. FOUCAULT, J.-F. LAFOND, R. ST-JACQUES, C. COPEMAN;
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Abstract: Various types of compounds are unable to efficiently cross the blood-brain barrier (BBB), or have too short of a half-life to reach their target across the BBB when administered systemically. Therefore, targeted delivery of drugs directly into specific brain compartments may be indicated. This can be achieved in rodents relatively easily as rats from a given strain are highly homogeneous and stereotaxic coordinates are well established. In large animals, accurate delivery in a given brain structure represents a greater challenge. Documented coordinates are considered approximations, because of marked variability in size and shape of the head. We investigated whether a combination of the published stereotaxic coordinates and cranial landmarks would allow us to develop a reliable approach for accurate intracerebral injection in the cynomolgus monkey. The putamen, the substantia nigra and the lateral ventricles were targeted for this initial project. The scalp was incised, and the position of the bregma relative to the instrumental zero was measured and documented. The coordinates of the areas of interest were located, marked and a burr hole was made to allow insertion of the needle. Various volumes of ink were injected at different rates to evaluate diffusion and reflux in order to determine an optimal administration volume range, size of needle and rate of injection. The animal was euthanized, sequential sectioning of the brain was performed and tissues were

embedded in paraffin and stained with hematoxylin and eosin for histopathological evaluation. The actual localization of the injection sites, ink diffusion and needle tracts was then confirmed by histopathology (substantia nigra and putamen) or by successful collection of cerebrospinal fluid (ventricles), and coordinates to be used were further refined based on the results observed. Once the optimal conditions were established, we proceeded with in-life bilateral injections in the putamen of a limited number of animals followed by an observation period. Clinical signs, body weights, food intake, neurological evaluations, and clinical pathology parameters were monitored for 3 weeks and detailed histopathology of the targeted structures was conducted to characterize any procedure-related effects. Reaching the substantia nigra proved to be more problematic than the other areas, and will require additional refinement of the procedures.

Disclosures: J. Douville: None. **F. Emond:** None. **C. Foucault:** None. **J. Lafond:** None. **R. St-Jacques:** None. **C. Copeman:** None.

Poster

595. Drug Delivery

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 595.03/J6

Topic: C.19. Drug Discovery and Development

Title: Application of polymeric nanoparticles for CNS targeted zinc delivery *in vivo*

Authors: *R. CHHABRA[1,2,3], B. RUOZI[4], A. VILELLA[5], S. PFAENDER[3,6], T. BOECKERS[6], M. ZOLI[5], G. TOSI[4], A. GRABRUCKER[3];
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Abstract: Alterations in zinc levels have been associated with various neurological and psychiatric disorders, such as schizophrenia, attention deficit hyperactivity disorder, depression, autism, Parkinson's disease, Alzheimer's disease, seizures and traumatic brain injury. However, the limited uptake of zinc into the brain owing to the presence of the blood-brain barrier, posses a serious challenge in selectively manipulating brain zinc levels for example by specific diets. Thus, in order to manipulate zinc-levels within the central nervous system (CNS) as tool for basic research and as emerging new therapeutic strategy for the prevention and treatment of psychiatric and neurological disorders, new approaches are highly desired. In this study, we

performed *in vivo* experiments investigating the possibility of targeted zinc delivery into the CNS using zinc-loaded polymeric nanoparticles conjugated with glycohexapeptide (g7), which are able to cross the blood-brain barrier. After administration of these nanoparticles, we evaluated the regional and time-dependent distribution of zinc and nanoparticles within the brain. Further, we investigated whether the delivery of zinc or the presence of nanoparticles *per se* alters the expression levels of zinc sensitive genes and proteins such as zinc transporters (ZnT and ZIP family members) and metallothioneins (MTs) and quantified possible toxic effects in terms of cell death. Our results reveal that zinc loaded g7-conjugated nanoparticles offer a promising strategy as a novel non - invasive approach to selectively enhance brain zinc levels within a small amount of time.

Disclosures: **R. Chhabra:** A. Employment/Salary (full or part-time):; International Graduate School in Molecular Medicine, Ulm University, Germany. **B. Ruozi:** None. **A. Vilella:** None. **S. Pfaender:** None. **T. Boeckers:** None. **M. Zoli:** None. **G. Tosi:** None. **A. Grabrucker:** None.

Poster

595. Drug Delivery

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Program#/Poster#: 595.04/J7

Topic: C.19. Drug Discovery and Development

Support: LLNL-15-023

Title: Targeted nanoproteinparticle conjugates for direct therapeutic shuttling to the brain

Authors: S. GILMORE, *M. W. MCNERNEY, N. FISCHER, N. BE, C. BLANCHETTE; Biosci. and Biotech. Div., Lawrence Livermore Natl. Lab., Livermore, CA

Abstract: Therapeutic delivery to the brain is challenging due to the limited permeability of the blood-brain barrier (BBB). Traditional therapeutics often cannot permeate the BBB, as it is composed of tightly apposed microvascular endothelial cells with specialized intercellular tight junctions, which severely limit transcellular traffic. To achieve successful passive traversal of the BBB, a compound must satisfy a specific range of physical properties, including low molecular weight, high lipophilicity, and very low levels of serum protein binding, which poses considerable issues in regards to drug design. However, there are active transport mechanisms such as transcytosis, whereby highly specific brain endothelial receptors complex with ligands, which can be exploited for targeted therapeutic delivery. Therefore, successfully delivery of therapeutics across the BBB can be achieved utilizing a platform that leverages this inherent

physiological mechanism. In this work, we examined the potential of using nanolipoprotein particles (NLPs) as a platform for targeted delivery of therapeutic compounds across the BBB. In initial screens of toxicity, the NLP platform was shown to display no signs of cytotoxicity against cultured brain endothelial cells. In addition, in cell uptake experiments, the NLP platform in the absence of any targeting ligands was shown to be rapidly taken up into human brain endothelial cells through endocytosis. To achieve targeted delivery across the BBB, three peptide ligands (TAT, G23 and Angiopep) that were previously shown to cross the BBB through transcytosis in a permeability assay using brain endothelial cells were selected and protocols for conjugation of these ligands to the NLP were developed. We are currently evaluating the effect of these targeting ligands on permeability across the BBB *in vitro* using an established BBB model and *in vivo* using a rat model. In these studies, a fluorophore will be encapsulated in the NLP and used as both a model drug therapeutic, and as a means to monitor BBB crossing through fluorescence detection. Such a platform has the potential to yield a tool providing essential drug delivery capacity relevant to a wide range of devastating neurological ailments. This work was performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07-NA27344. Lawrence Livermore National Security, LLC

Disclosures: S. Gilmore: None. **M.W. McNerney:** None. **N. Fischer:** None. **N. Be:** None. **C. Blanchette:** None.

Poster

595. Drug Delivery

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 595.05/J8

Topic: C.19. Drug Discovery and Development

Title: Guanidinoglycoside conjugation; a novel technology for intranasal delivery of therapeutic proteins to the CNS

Authors: *C. GLASS[1], B. E. THACKER[1], W. TONG[2], K. M. HAMILL[3], C. A. DWYER[2], J. J. PHILLIPS[4], Y. TOR[3], T. SCOTT[5], J. D. ESKO[2];
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Abstract: Treating central nervous system (CNS) disorders is difficult because the blood brain barrier (BBB) restricts delivery of drugs to the brain. Less than 1% of most drugs reach the CNS

resulting in a lack of available treatments for many CNS diseases such as stroke, neurodegenerative diseases and brain tumors. Many high molecular weight molecules such as antibodies show promise in treating CNS diseases based on *in vitro* systems and animal models; however, high molecular weight substances are severely restricted from crossing the BBB. Intraparenchymal, intraventricular and intrathecal injection/infusion can deliver therapeutics directly to the CNS but these routes are invasive and impractical for long-term recurrent delivery. Intranasal administration, drug delivery across the nasal epithelium into the brain, is an alternative route. The major disadvantage is that limited absorption across the nasal epithelium has restricted the application to compounds that are highly potent, typically hydrophobic and low molecular weight. To address the problem of intranasal protein delivery to the brain, TEGA has developed a patented technology that involves chemically conjugating glycosides to therapeutic agents (proteins and other agents). Glycoside conjugation is a platform technology that facilities the rapid transport of proteins (≥150 kDa) to the brain through the nasal epithelia following intranasal administration. We have conjugated a number of proteins including enzymes and antibodies and assessed them for intranasal CNS delivery. Conjugated iduronidase and sulfamidase, enzymes missing in Hurler's (MPSI) and Sanfilippo syndromes (MPSIIIA), were well tolerated by intranasal administration, and rapidly achieved enzyme activities equal to or greater than wildtype levels in MPSI and MPSIIIA mouse brains, and significantly reduced the levels of toxic substrate. We have also improved the delivery of therapeutic anti-EGFR antibodies for glioblastoma, a deadly malignant brain tumor. Glycoside conjugated antibodies retained their EGFR binding properties and their potency to inhibit cultured glioma progenitor cell growth. In mice, high levels of the conjugated antibody were rapidly achieved in the olfactory bulb, whereas, the unconjugated antibody was ten-fold less. Immunohistological staining revealed the conjugated antibody in the interior granule layer.

Disclosures: **C. Glass:** A. Employment/Salary (full or part-time):; TEGA Therapeutics, Inc. **B.E. Thacker:** A. Employment/Salary (full or part-time):; TEGA Therapeutics, Inc. **W. Tong:** None. **K.M. Hamill:** None. **C.A. Dwyer:** None. **J.J. Phillips:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; TEGA Therapeutics, Inc. **Y. Tor:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TEGA Therapeutics, Inc. **T. Scott:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TEGA Therapeutics, Inc. **J.D. Esko:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); TEGA Therapeutics, Inc..

Poster

595. Drug Delivery

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Pharmaceutical Research and Manufacturers of America (PhRMA) Foundation

University of Wisconsin-Madison School of Pharmacy

University of Wisconsin-Madison Graduate School

Title: Visualizing normal and enhanced distribution of antibodies and antibody fragments in brain extracellular space using *in vivo* integrative optical imaging

Authors: *D. J. WOLAK[1,2], E. BRUNETTE[6], D. B. STANIMIROVIC[6], R. G. THORNE[1,2,3,4,5]; [1]Pharmaceut. Sci., [2]Clin. Neuroengineering Training Program, [3]Neurosci. Training Program, [4]Cell. and Mol. Pathology Grad. Program, [5]Inst. for Clin. and Translational Res., Univ. of Wisconsin-Madison, Madison, WI; [6]Inst. for Biol. Sci., Natl. Res. Council of Canada, Ottawa, ON, Canada

Abstract: The precise factors governing the transport of antibody-based drugs within the CNS are not yet understood, despite their potential use as central immunotherapies. The blood-brain barrier limits drug delivery following systemic administration but a lesser studied barrier that affects both systemic and centrally applied drugs is the tissue hindrance associated with drug diffusion through the tortuous brain extracellular space (ECS). We have used a highly validated method, integrative optical imaging (IOI; Nicholson & Tao. *Biophys J*, 1993), in order to define key protein characteristics that affect their extracellular diffusion in brain tissue (e.g. size, binding). We recently reported that full length IgG (150 kDa) diffusion is ~10-fold lower in brain than in free medium (Wolak, Pizzo & Thorne. *J Control Release*, 2015) and attributed this finding to size-dependent restricted diffusion due to the small (40-60 nm) brain ECS width (Thorne & Nicholson. *PNAS,* 2006) as well as receptor binding (Thorne & Nicholson. *PNAS,* 2008). Here, we investigated extracellular diffusion in brain by carefully studying the variation of diffusional hindrance across antibody tracers of different size as well as the effect of hyperosmolar mannitol solutions on the different tracers. We used *in vivo* IOI to measure the diffusion coefficients of proteins ranging from full length IgG (~150 kDa) to smaller Fab fragments (~50 kDa) to much smaller single domain antibodies (sdAb; ~15 kDa). Free diffusion

(D) was measured in dilute agarose gel and the effective diffusion coefficient (D^*) was measured in the somatosensory cortex of anesthetized rats using an open cranial window. As expected, the larger IgG diffused more slowly [$D = 6.56 \pm 0.22 \times 10^{-7}$ cm^2/s (mean ± SE; $n = 20$)] than the smaller sdAb [$D = 14.5 \pm 0.4 \times 10^{-7}$ cm^2/s ($n = 35$)] in free solution. Comparing free diffusion to diffusion in brain, we observed that IgG experienced much more diffusional hindrance to its distribution in brain than the sdAb (IgG $D/D^* \sim 7.5$; sdAb $D/D^* \sim 4.5$). Co-injection with 0.75 M mannitol significantly reduced the diffusional hindrance of both IgG and sdAb in brain (IgG $D/D^* \sim 4.7$; sdAb $D/D^* \sim 3.5$), but the relative increase in D^* was greater with mannitol for the larger IgG (67%) than for sdAb (31%). We hypothesize that the co-injected mannitol rapidly redistributed water into the ECS from intracellular compartments, enabling the larger IgG to diffuse more effectively through a widening of the ECS. Our results provide the first *in vivo* diffusion measurements for antibody fragments as well as the first quantitative measurements of antibody diffusion in the brain extracellular space using an osmotic approach to enhance distribution.

Disclosures: D.J. Wolak: None. **E. Brunette:** None. **D.B. Stanimirovic:** None. **R.G. Thorne:** None.

Poster

595. Drug Delivery

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 595.07/J10

Topic: C.19. Drug Discovery and Development

Support: EXIST-Forschungstransfer

Title: Lipid DNA-nanoparticles as drug carrier for the treatment of eye diseases

Authors: *S. O. SCHNICHELS[1], J. HURST[1], A. GRUSZKA[1], K. BARTZ-SCHMIDT[1], A. HERRMANN[2], M. S. SPITZER[1], J. DE VRIES[1];
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Abstract: Purpose: Currently most eye diseases are treated with multiple daily doses of highly concentrated eye drops. Treatment is severely hindered because only approximately 1-5% of the applied drug stays on the eye long enough to be effective. Due to the high concentration of the drug often systemic and local side effects are caused. Additionally, the repeated application of eye drops generally cause a reduced compliance. Methods: We developed a drug carrier for eye

drops based on lipid-DNA nanoparticles (NPs). This NP can be loaded through several different binding possibilities. To evaluate the NP, they were conjugated to a fluorescent marker and dropped on rat eyes and human corneal tissue. Afterwards the eyes were processed and analyzed for binding. To exclude toxicity our NPs were tested in-vitro and in-vivo. As a first drug kanamycin B was conjugated to the NPs. The uptake of the kanamycin-NPs was tested on human corneal tissue. Additionally, the functionality of pristine and NP-kanamyicn was evaluated in-vitro in a minimum inhibitory concentration test. To prove functionality at the site of action, corneas of eyes treated with our kanamycin-NP or pristine kanmycin were transferred to petrifilms infected with E. coli. Results:The NP showed excellent binding to the cornea epithelium compared to their small molecule counterparts. They were even found up to 4h after application to conscious rats. Most importantly, the NPs also show a high affinity for the human cornea. In addition, our NP did not show any cytotoxicity at the used concentration for our applied NP eye drops neither in-vivo nor in-vitro. Both kanamycin alone and the loaded AB-NPs were able to decrease the amount of colonies compared to the untreated corneas. Even more important, our NPs were still hindering E.coli growth after 30 min of washing, whereas the free antibiotic already lost its effectiveness after 5 min. Conclusion: In conclusion, using this novel carrier system we are able to significantly increase the adherence time of the drug on the eye. Most important is, that the drug tested was still pharmaceutically active. As a consequence, a lower frequency of eye drop administration is feasible which is beneficial for the compliance and treatment of the patient. Additionally, a lower drug concentration can be used, what drastically reduces systemic and local side effects. Another favorable feature of the delivery system is that drugs currently not in use due to their severe side effects could become utilized again.

Disclosures: **S.O. Schnichels:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor (IP is with the University). Other; Research prizes from Novartis and Alcon. **J. Hurst:** None. **A. Gruszka:** None. **K. Bartz-Schmidt:** None. **A. Herrmann:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor (IP is with the University). **M.S. Spitzer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor (IP is with the University). Other; Research prizes from Novartis and Alcon. **J. de Vries:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor (IP is with the University).

Poster

595. Drug Delivery

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 595.08/J11

Topic: C.19. Drug Discovery and Development

Support: Pioneer Research Center Program through the National Research Foundation of Korea 2012-0009524

NRF 2011-00313832010-0029690

Title: Guidance of magnetic nanocontainers for treating Alzheimer's disease using an electromagnetic, targeted drug-delivery actuator

Authors: G.-H. YOON[1], F. UL AMIN[1], J. YOON[2], *M.-O. KIM[1];
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Abstract: The "impermeability" of the blood-brain barrier (BBB) has hindered effective treatment of central nervous system (CNS) disorders such as Alzheimer's disease (AD), which is one of the most common neurodegenerative disorders. A drug can be delivered to a targeted disease site effectively by applying a strong electromagnetic force to the conjugate of a drug and magnetic nanocontainers. This study developed a novel nanotechnology-based strategy to deliver therapeutic agents to the brain via the BBB as a possible therapeutic approach for AD. First, a novel approach for an electromagnetic actuator for guiding nanocontainers is introduced. Then, we analyzed the *in vivo* uptake in mice experimentally to evaluate the capacity of the nanocontainers. In the mouse model, we demonstrated that magnetic particles can cross the normal BBB when subjected to external electromagnetic fields of 28 mT (0.43 T/m) and 79.8 mT (1.39 T/m). Our study also assessed the differential effects of pulsed (0.25, 0.5, and 1 Hz) and constant magnetic fields on the transport of particles across the BBB in mice injected with magnetic nanoparticles (MNPs) via a tail vein. The applied magnetic field was either kept constant or pulsed on and off. Relative to a constant magnetic field, the rate of MNP uptake and transport across the BBB was enhanced significantly by a pulsed magnetic field. Localization inside the brain was established using fluorescent MNPs. These results using 770-nm fluorescent carboxyl magnetic nanocontainers demonstrated the feasibility of the proposed electromagnetic targeted drug delivery actuator. These results establish an effective strategy for regulating the biodistribution of MNPs in the brain through the application of an external electromagnetic field. This might be a valuable targeting system for AD diagnosis and therapy.

Disclosures: G. Yoon: None. **F. Ul Amin:** None. **J. Yoon:** None. **M. Kim:** None.

Poster

595. Drug Delivery

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 595.09/J12

Topic: C.19. Drug Discovery and Development

Support: NSERC

NINT-NRC

WCHRI

AIHS

Alberta-Gangwon

University of Alberta Engineering

Davey Fund for Brain Research

Title: Self-assembling MMP-2 cleavable hydrogel drug delivery systems; neural tissue biocompatibility and response

Authors: *K. M. KOSS[1], M. A. CHURCHWARD[2], K. G. TODD[3], L. D. UNSWORTH[1]; [1]Chem. and Materials Engin., [2]Psychiatry, [3]Univ. of Alberta, Edmonton, AB, Canada

Abstract: In the event of neural tissue injury, neurotrophic factor peptide analogues are capable of promoting healing by increasing neurogenesis, promoting neuronal survival and attenuating glial activation. Peptides have been considered as ideal therapeutic agents as they are specific, potent, small, and diffuse readily. However, peptides are also digested and short lived, making their *in vivo* delivery difficult. The self-assembling peptide $(RADA)_4$ is a novel class of peptide that, upon injection, assemble into a 3D hydrogel nanofiber matrix, capable of storing water and molecules. Synthesizing peptide therapeutics onto $(RADA)_4$ can afford protection from circulating proteases and utilizing matrix metalloproteinase-2 (MMP-2) cleavage sequences allows an 'on-demand' and local tissue release strategy. Understanding self-assembly, controlled release of bound therapeutics, biocompatibility, and tissue response is vital for successful clinical application. In this study, $(RADA)_4$-GG-GPQG+IASQ (CS1) and $(RADA)_4$-GG-GPQG+PAGQ (CS2), known for high and low MMP-2 sensitivity, respectively, were investigated. The '+' denotes the scissile bond. Neuropeptides DGGL, a ciliary neurotrophic factor analogue, and MVG, a brain-derived neurotrophic factor secretion stimulant, were tethered to the c-termini. $(RADA)_4$-IKVAV was explored to promote glial adhesion and biocompatibility. Nanofiber matrices were present in all samples, visualized using TEM, suggesting efficient formation of drug delivery matrices. Cleavage of bioactive peptides by MMP-2 was monitored over time, and

showed expected product formation, using MALDI-TOF mass spectrometry, for both the high and low activity cleavage sequences. Microglia seeded onto $(RADA)_4$ matrices retained a ramified morphology, and showed increased adhesion, survival, and proliferation but did not increase markers of inflammation, suggesting good biocompatibility. The MMP-2 cleaved drug fragments promoted neurogenesis in PC-12 cells, observed by neurite extension and increased acetylcholine esterase activity, and these cells increased seeding capacity with the addition of $(RADA)_4$-IKAV. Overall, the $(RADA)_4$ system has been demonstrated as a self-assembling tuneable drug release system with good neural tissue biocompatibility and response. In this system, neurotrophic peptide delivery is balanced to surrounding cell and tissue activity, and may have a greater impact as a potential therapy for many sources of neural tissue injury.

Disclosures: K.M. Koss: None. **M.A. Churchward:** None. **K.G. Todd:** None. **L.D. Unsworth:** None.

Poster

595. Drug Delivery

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 595.10/J13

Topic: C.03. Parkinson's Disease

Title: Effect of intranasal administration of encapsulated gdnf in an animal model of Parkinson´s disease

Authors: O. GARTZIANDIA[1,2], E. HERRÁN[1,2], *J. A. RUIZ-ORTEGA[3,4], C. MIGUELEZ[3,4], M. IGARTUA[1,2], J. V. LAFUENTE[5], J. L. PEDRÁZ[1,2], L. UGEDO[4], R. M. HERNÁNDEZ[1,2]; [1]NanoBioCel Group.Laboratory of Pharmaceutics.Pharmacy School.University of The Basque Country (UPV/EHU), Vitoria-Gasteiz, Spain; [2]Biomaterials and Nanomedicine (CIBER-BBN). Biomed. ResearchNetworking Ctr. in Bioengineering, Vitoria-Gasteiz, Spain; [3]Dpt.Pharmacology.University Basque Country.UPV/EHU, Vitoria-Gasteiz, Spain; [4]Dept.Pharmacology. Fac. of Med. and Denstistry. Univ. of the Basque Country (UPV/EHU), Leioa, Spain; [5]LaNCE. Dept.Neurosciences. Fac. of Med. and Denstistry. Univ. of the Basque Country (UPV/EHU), Leioa, Spain

Abstract: Neurotrophic factors, such as the glial cell- derived neurotrophic factor (GDNF), are promising alternatives to treat Parkinson's Disease (PD). However, their short half-life and rapid degradation after *in vivo* administration has limited the clinical use. Recently, the intranasal delivery has appeared as an alternative to release GDNF directly to the brain. The aim of this study was to evaluate the *in vivo* neuroprotective effect of intranasally administered GDNF,

encapsulated in Chitosan-nanostructured lipid carriers (CS-NLCs), in a 6-hydroxydopamine (6-OHDA) rat model. 6-OHDA lesion procedures in rats were performed according to previous protocols and CS-NLCs were prepared by melt-emulsification technique. After the lesion, rats were randomly divided into four groups (5 rats/group): Sham, CS-NLCs-without GDNF, CS-NLCs loaded with GDNF (2.5 µg GDNF/day) and GDNF in PBS solution (2.5 µg GDNF/day) and intranasal administration was done during two weeks. The *in vivo* effectiveness of the intranasal administration of GDNF administration was tested by the amphetamine-induced rotational behaviour test during 7 consecutive weeks and by the cylinder test in three times during the study. At the end of the study, the degree of dopamine denervation in the striatum and substantia nigra compacta (SNc) was analyzed using a Tyrosine Hydroxylase (TH) immunostaining and a correlation analysis was done. CS-NLC-GDNF group showed significantly lower rotations per minute with respect to the basal number of rotations from the 3rd testing session until the end of the study where a reduction of 80% was achieved ($p<0.05$, repeated measures two-way ANOVA). The other groups included showed stable rotational behaviour thorough the 7 weeks of the study. Similar results occurred in the cylinder test where a reduction of forelimb asymmetry ($p<0.05$, repeated measures two-way ANOVA) was found in the CS-NLCs loaded with GDNF group. Also, a significant correlation was observed between rotational and cylinder test performances with both optical density in the striatum and neuronal density in the SNc of the rats. These results demonstrate that the administration of CS-NLCs loaded with GDNF by intranasal route, induces an improvement in the degree of injury in the striatum and SNc of the ipsilateral hemisphere of the lesioned rat brain, and suggest that it could be a promising therapy for the treatment of PD. Support by Saiotek S-PE13UN048, Ministerio de Economía y Competitividad SAF2013-42347-R, Ministerio de Sanidad FIS PI12/00613 and UPV/EHU UFI 11/32. O. G.has a fellowship from the UPV/EHU.

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Poster

596. Auditory Processing: Cortex and Cortical Circuits

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 596.01/J14

Topic: D.02. Auditory System

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Title: Changes in birdsong production and electrophysiological activities in HVC after the whole lesion of Nucleus Uvaeformis in adult Bengalese Finches

Authors: *R. WANG[1], F. WU[1], X. ZHANG[2], X. ZHANG[2], S. ZENG[1];
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Abstract: Birdsong is a learned bebavior, which has been regarded as the best useful model to study the neural mechanism underlying song learning. High vocal center(HVC) in the telecephalon integrates sensory and motor activity and plays an essential role in birdsong learning and production. The thalamus nucleus Uva, which receives input of auditory information and projects to HVC directly or via telencephalic nucleus interface(Nif) indirectly. Available literature concerning Uva actions in birdsong learning and production is focused on the song behavior changes by injuring Uva, or on the relationship between the firing activities in Uva and HVC. Here we first injured the whole Uva bilaterally in the adult Bengalese Finches(Lonchura domestica). We then compared the song changes before and after lesion. We next made extracellular recording of HVC *in vivo* in normal and Uva injured birds to find out the changes in firing activities within the three types of HVC neurons (interneurons, RA (the robust nucleus of the arcopallium)-projecting or Area X projecting neurons). Finally, we injected fluorescent tracer into the normal HVC, resulting in retrogradely labeled HVC-projecting cells in Uva and Nif. This tracing technique combined with immunohistochemistry for several neurotransmitters or receptors, is allowed us to determine what neurotransmitters are used by HVC projecting cells in Uva and NIf. Our results indicated that: 1) Birdsongs degraded severely and permanently at least 3 months after Uva lesion. Several phrases were deleted (only phrase C was remained), and the amplitude and frequency of the remained phrases largely decreased. These data suggest that Uva is necessary for normal song production; 2) Following Uva lesion, the firing rates in HVC interneuron showed a significant increase, whereas they did not change significantly in RA or Area X -projecting cells, suggesting that HVC activity is inhibited by Uva interneurons; 3) TH (Tyrosine hydroxylase), GABA (γ-aminobutyric acid), NMDAR(N-methyl-d-aspartate receptor) and GABAA receptor are widely distributed in HVC-projecting cells in Uva and Nif. However, the percentage of GABA in Uva was higher than in NIf. These results are useful to further understand the function of Uva in song learning and production.

Disclosures: **R. Wang:** None. **F. Wu:** None. **X. Zhang:** None. **X. Zhang:** None. **S. Zeng:** None.

Poster

596. Auditory Processing: Cortex and Cortical Circuits

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 596.02/J15

Topic: D.02. Auditory System

Support: University of Virginia

Title: Intrinsically phasic and tonic excitatory neurons in the avian auditory mesopallium

Authors: ***A. N. CHEN**[1], C. D. MELIZA[1,2];
[1]Neurosci. Grad. Program, Univ. of Virgi, Charlottesville, VA; [2]Psychology, Univ. of Virginia, Charlottesville, VA

Abstract: The caudal mesopallium (CM) is a telencephalic area in the avian auditory pathway where selective, invariant representations of learned conspecific song emerge. Hodological, functional, and gene expression data suggest that CM may be analogous or homologous to superficial neocortical layers, but the intrinsic physiological properties of CM neurons have not been investigated. Using whole-cell recordings from brain slices of juvenile and adult zebra finches (Taeniopygia guttata), we identified several classes of neurons in CM with distinct spike shapes, frequency-current relationships, and adaptation profiles. Many neurons (26%) resembled regular-spiking neurons in the neocortex, with relatively broad action potentials and with spike-frequency adaptation over prolonged depolarizations. A smaller proportion of cells (8%) had narrow spikes and little to no frequency adaptation, characteristics of inhibitory interneurons. However, the majority of neurons (66%) had broad action potentials and exhibited profound adaptation, only firing 1-5 times at the onset of depolarization. Onset-spiking neurons were present in adults, and their properties persisted in the presence of fast synaptic transmission blockers. To our knowledge, intrinsic onset-only responses have not been reported in the mammalian cortex. A subset of neurons were filled with biocytin in order to correlate cell morphology with physiology. Based on responses to complex, broadband current injections, onset- and regular-spiking neurons have different temporal integration properties and are thus likely to fulfill different functions in processing spectrotemporally rich auditory signals.

Disclosures: **A.N. Chen:** None. **C.D. Meliza:** None.

Poster

596. Auditory Processing: Cortex and Cortical Circuits

Location: Hall A

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Program#/Poster#: 596.03/J16

Topic: D.02. Auditory System

Support: NIH R01 NS082179

Title: Multifaceted modulation of auditory signal detection and encoding by norepinephrine: Evidence for differential adrenergic receptor mediation

Authors: *M. IKEDA[1], M. LIMA[2], L. REMAGE-HEALEY[2];
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Abstract: In mammalian auditory cortex, norepinephrine enhances auditory detection (measured by signal-to-noise ratio) and frequency tuning for relatively simple stimuli, such as tones and calls. However, the role of norepinephrine in high order processing of complex syntactical auditory stimuli is not clear. Previously, in one region of the songbird auditory cortex, we showed that norepinephrine enhances the signal-to-noise ratio to auditory stimuli by decreasing spontaneous firing activity, similar to the mammalian auditory cortex. Interestingly, norepinephrine also enhances the decoding accuracy of an algorithm that classifies spike trains based on spiking frequency. Here, we further tested whether the enhancement in classification accuracy was due to changes in spike timing and/or changes in the number of spikes. In addition, we tested the effect of adrenergic agonists to determine which adrenergic receptors mediate the effects of norepinephrine. We found that norepinephrine significantly enhanced the performance of a pattern classifier that solely depended on spike timing patterns. In addition, an alpha-2 adrenergic agonist, clonidine, mimicked the effects of norepinephrine on spontaneous firing and signal-to-noise ratio, whereas an alpha-1 adrenergic agonist did not. Interestingly, in contrast to norepinephrine, clonidine did not enhance the performance of either pattern classifier. Together, our findings suggest that norepinephrine enhances both auditory detection and auditory coding by altering spiking pattern and the number of spikes. Moreover, the enhancement in signal detection is likely to be mediated by alpha-2 adrenergic receptors while the change in spike patterning itself may be mediated by other receptor sub-types.

Disclosures: **M. Ikeda:** None. **M. Lima:** None. **L. Remage-Healey:** None.

Poster

596. Auditory Processing: Cortex and Cortical Circuits

Location: Hall A

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Program#/Poster#: 596.04/J17

Topic: D.02. Auditory System

Support: NSF IOS #1257891

Title: Thalamocortical connections of sensory areas in the nine-banded armadillo (Dasypus novemcinctus)

Authors: *H. A. LAWRENCE, A. BUCK, J. J. PADBERG;
Biol., Univ. of Central Arkansas, Conway, AR

Abstract: In order to identify features of neural organization that may be common across mammalian clades, we are conducting a series of studies examining the sensory areas of a representative species of Xenarthra, a relatively early branch of the mammalian lineage. The nine-banded armadillo (Dasypus novemcinctus) is the only extant xenarthran species found in North America. We are currently exploring the connectional organization of D. novemcinctus by placing electrophysiologically guided injections of fluorescent retrograde neuroanatomical tracers into the sensory cortex, and reconstructing connectional patterns using the Neurolucida imaging software. Labeled cells and terminals in the thalamus resulting from the injections were related to architectonic boundaries as identified based upon cytochrome oxidase (CO) histochemistry or Nissl staining. In CO series, the ventroposterior nucleus is segregated into a medial portion, which is moderate to dense in staining intensity and relatively homogenous, and a lateral portion, which is densely stained and interrupted by small fiber bundles. The ventrolateral nucleus, located dorsal to the ventroposterior lateral nucleus, is lighter staining and homogenous. The lateral geniculate is densely stained and relatively small, while the medial geniculate is densely stained and occupies a large dorsolateral extent of the posterior thalamus. Following injections of .0.3-0.4 μL of tracers (Alexa-Flour 555 conjugated to 10kD dextrans, or Alexa-Fluor 555 conjugated to CTB) placed into the snout representation of primary somatosensory cortex, dense clusters of labeled neurons were identified in the dorso-lateral portion of the medial ventral posterior nucleus, and less dense labeling was observed in the ventrolateral nucleus. This pattern of neuroanatomical organization is consistent with that reported for all other mammalian clades that have been studied, from monotremes to Euarchontoglires, suggesting an origin in a common mammalian ancestor. Furthermore, in this case, unique morphological specializations such as the presence of ossified armor appear to have relatively little impact on the basic mammalian organization of sensory outputs from the thalamus to cortex.

Disclosures: **H.A. Lawrence:** None. **A. Buck:** None. **J.J. Padberg:** None.

Poster

596. Auditory Processing: Cortex and Cortical Circuits

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Topic: D.02. Auditory System

Support: NIH Grant 1F31DC013976-01

Title: Anatomical and functional convergence of motor and neuromodulatory synapses in mouse auditory cortex

Authors: ***A. NELSON**, R. MOONEY;
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Abstract: We recently characterized a projection from the secondary motor cortex (M2) to the auditory cortex (ACtx) of the mouse and established that this pathway is an important source of signals that modulate auditory cortical activity in a movement-dependent manner. We hypothesize that this circuit provides motor-related corollary discharge signals to the ACtx and that these signals can be shaped by experience to form associations between the animal's movements and the reafferent sounds resulting from these movements. To better understand how this motor to auditory cortical circuit interacts with neuromodulatory circuits implicated in auditory cortical plasticity, we have begun to explore the relationship between motor cortical synapses and cholinergic synapses in the ACtx. Using intersectional monosynaptic viral tracing methods, we established that cholinergic neurons in the basal forebrain (BF_ACh) innervate all of the auditory cortical cell types that receive input from M2, and that a subset of BF neurons provide input to both M2 and the ACtx. Using anterograde viral tracing methods, we found that BF_ACh and M2 terminals are co-mingled across all layers of the ACtx. Using optogenetic circuit mapping methods in brain slices, we further established that BF_ACh synapses activate both nicotinic and muscarinic receptors on inhibitory and excitatory cells in the ACtx and thus can drive feedforward inhibition onto excitatory cells in the ACtx, further resembling M2 inputs in their functional properties. By using a combination of electrophysiological, pharmacological, and optogenetic methods in brain slices, we also established that BF_ACh and M2 axons provide convergent input onto single auditory cortical neurons. Finally, using *in vivo* multiphoton calcium imaging methods in freely behaving mice, we established that BF_ACh axon terminals in the ACtx display movement-related activity patterns that closely parallel M2 terminal activity patterns. Therefore, motor cortical and cholinergic inputs to the ACtx are coactive during

movement, and these inputs converge postsynaptically to influence single neurons in the ACtx. This functional convergence may be important for gating and modifying corollary discharge signals in the ACtx in a task- and experience-dependent manner.

Disclosures: A. Nelson: None. **R. Mooney:** None.

Poster

596. Auditory Processing: Cortex and Cortical Circuits

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Topic: D.02. Auditory System

Support: NIH DC008983

NIH EY019049

Title: Thalamocortical innervation pattern in mouse auditory and visual cortex: laminar and cell-type specificity

Authors: *L. MESIK[1], X.-Y. JI[2], B. ZINGG[3], Z. XIAO[2], L. ZHANG[3], H. W. TAO[3];
[1]Unifersity of Southern California, Los Angeles, CA; [2]Southern Med. Univ., Guangzhou, China; [3]USC, Los Angeles, CA

Abstract: Despite many previous studies, the functional innervation pattern of thalamic axons and their target specificity remains to be investigated thoroughly. Here, in primary auditory cortical slices, we examined thalamic innervation patterns for excitatory and different types of inhibitory neurons across laminae, by optogenetically stimulating axons from the medial geniculate body (MGB). We found that excitatory cells and parvalbumin (PV)-expressing inhibitory neurons across layer 2/3 (L2/3) to L6 are directly innervated by thalamic projections, with the strongest innervation occurring in L4. The innervation of PV neurons is stronger than that of excitatory neurons in the same layer, with a relatively constant ratio between their innervation strengths across layers. For somatostatin (SOM) and vasoactive intestinal peptide (VIP) inhibitory neurons, essentially only L4 neurons were innervated by thalamic axons and the innervation was much weaker compared to excitatory and PV cells. In addition, more than half of inhibitory neurons in L1 were innervated, relatively strongly, by thalamic axons. Similar innervation patterns were also observed in the primary visual cortex. Thus, thalamic information can be processed independently and differentially by different cortical layers, in addition to the generally thought hierarchical processing starting from L4. This parallel processing is likely

shaped by feedforward inhibition from PV neurons in each individual lamina, and may extend the computation power of sensory cortices.

Disclosures: **L. Mesik:** None. **X. Ji:** None. **B. Zingg:** None. **Z. Xiao:** None. **L. Zhang:** None. **H.W. Tao:** None.

Poster

596. Auditory Processing: Cortex and Cortical Circuits

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Topic: D.02. Auditory System

Support: International Anesthesia Research Society (MRA to AR)

NIH Grant DC006013-01 to MIB

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UW Department of Anesthesiology

Title: Pathway specific effects of isoflurane on synaptic responses in supra- and infra-granular auditory cortex neurons

Authors: ***A. RAZ**[1], B. M. KRAUSE[1,2], S. M. GRADY[1], M. I. BANKS[1];
[1]Dept. of Anesthesiol., Univ. of Wisconsin, Madison, WI; [2]Neurosci. Training Program, Univ. of Wisconsin - Madison, Madison, WI

Abstract: Introduction: The mechanisms underlying loss of consciousness (LOC) under anesthesia remain an enigma. We have previously shown that cortico-cortical (CC; “top-town”) extracellular synaptic responses are preferentially suppressed by isoflurane (ISO) compared to thalamo-cortical (TC; “bottom-up”) responses. This result is consistent with a model in which anesthesia causes LOC by interfering with predictive coding in cortex via selective inhibition of top-down connections. Here, we investigate the mechanism underlying this differential effect by measuring the effect of ISO in clinically relevant concentrations on the post-synaptic responses of cortical supra- and infra-granular (SG, IG) layer neurons to TC and CC stimuli. Methods: The study was approved by the institutional animal care and use committee. Acute auditory TC brain slices were prepared from 4-8 week-old mice. Afferent stimuli were applied using bipolar tungsten electrodes either at the superior thalamic radiation, just rostral to the hippocampus or in layer 1 or 2 (L1/L2) of neocortex, 0.5 - 1 mm rostral to the recording site in auditory cortex.

Cortical neurons, either from layer 5-6 (IG), or from layer 2-3 (SG), were identified visually. Short latency (presumably monosynaptic) TC and CC synaptic responses and responses to polarizing current pulses were recorded under whole cell current clamp. ISO (1%) was dissolved in the aCSF and bath applied to the slice. We compared peak TC and CC EPSP amplitude, as well as resting membrane potential (ERest), membrane resistance (RIn), and spike threshold (VTh) with and without ISO in SG and IG cells. Results: There was no significant effect of ISO on ERest or RIn . VTh increased in both cell types, but the effect was significant only for SG cells (IG: control -33.9±23.8mV ISO -29.5±18.9, p=0.09 paired t-test, n=15 cells; SG: control -34.0±7.4mV ISO -23.0±12.0mV, p=0.01 paired t-test, n=7). Under ISO, TC responses did not decrease significantly: 15.4% (p=0.1 t-test, n=15) and 4.7% (p=0.56 t-test, n=8) decrease in SG and IG responses respectively, whereas CC responses were decreased by 54.8% (p<0.001 t-test, n=15) and 54.7% (p<0.001 t-test, n=8) in SG and IG respectively. Conclusions: Our observation of differential sensitivity of TC versus CC synaptic responses is consistent with previous reports of selective effects of anesthetics on top-down connections in cortex. Because we did not observe changes in RIn, we suggest that the underlying mechanism for this pathway specificity is either selective effects on glutamate release at CC synapses or differential engagement of local inhibitory circuits.

Disclosures: **A. Raz:** None. **B.M. Krause:** None. **S.M. Grady:** None. **M.I. Banks:** None.

Poster

596. Auditory Processing: Cortex and Cortical Circuits

Location: Hall A

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Topic: D.02. Auditory System

Support: CIHR Operating Grant

NSERC CGS Master's Scholarship

FRQNT Doctoral Research Scholarship

Title: Modulating auditory cortical plasticity through passive exposure to amplitude-modulated noise

Authors: ***M. THOMAS**, M. CISNEROS-FRANCO, L. OUELLET, E. DE VILLERS-SIDANI; McGill University, Montreal Neurolog. Inst., Montreal, QC, Canada

Abstract: Cortical representations of the external world are shaped by sensory experience at a young age and preserved through the stabilization of inhibitory networks. These representations are largely thought to remain stable throughout the lifetime, but recent work has shown that sensory deprivation in adulthood, such as dark-rearing, is capable of returning sensory cortices to an immature and disinhibited state. Here, we draw a parallel between sensory deprivation and exposure to continuous white noise. Housing adult rats in white noise, which masks normal environmental sounds without damaging the auditory system, has been found to have a profound disinhibitory effect on the auditory cortex, however the mechanisms behind this effect remain unclear. We argue that similar to sensory deprivation, the prolonged absence of salient auditory signals in noise exposure is the trigger for disinhibition and subsequent induction of cortical plasticity. In the following experiments, we tested this hypothesis by passively exposing adult Long-Evans rats to white noise of different degrees of amplitude modulation. In this manner, we were able to vary the signal-to-noise ratio of the exposure from 0% (no modulation) to 100% (strong modulation). Specifically, we exposed four groups of rats to two weeks of 70 dB broadband noise modulated at a rate of 3 Hz and a depth of 0%, 25%, 50% or 100%. A fifth group of naive rats was housed under standard conditions. At the end of this period, we recorded auditory neuronal responses from the anesthetized rats using multi-electrode arrays and performed immunohistochemical staining on post-mortem tissue slices of the primary auditory cortex. For rats exposed to 0% modulated noise, we observed an increase in cortical plasticity in accordance with previous studies. Evidence of neural disinhibition included a higher spontaneous firing rate, a shorter response latency to pure tones, and sensitization to trains of repeated tones. These variations were significantly less profound in rats exposed to modulated noise, with the magnitude of these changes decreasing with greater depth of modulation. Immunohistochemistry results showed a pronounced increase in excitatory cellular activity as measured by c-fos expression for rats exposed to 0% modulated noise, along with a step-wise decrease in expression for 25%, 50%, and 100% noise-exposed rats. Our results suggest that the absence of auditory signals is a key factor in plasticity following chronic noise exposure. This is an important step in understanding how sensory deprivation leads to cortical disinhibition and will underlie future studies on therapeutic applications of induced sensory plasticity.

Disclosures: **M. Thomas:** None. **M. Cisneros-Franco:** None. **L. Ouellet:** None. **E. de Villers-Sidani:** None.

Poster

596. Auditory Processing: Cortex and Cortical Circuits

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Support: Nakatani Foundation for Advancement of Measuring Technologies in Biomedical Engineering

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JSPS KAKENHI Grant Numbers 15H02772 and 15K1209127

Title: Spatial distribution patterns of short term potentiation induced by microelectrode stimulation in the mouse auditory cortex *in vitro*

Authors: *T. TATENO, A. SANO;
Hokaido Univ., Sapporo, Japan

Abstract: All sensory cortical areas, including the auditory areas, are considered to be wired according to the same general schema, often referred to as the canonical model of cortical circuitry. The auditory cortex (AC) *in vivo*, however, is functionally anisotropic; the functional organization along the tonotopic axis is qualitatively different from that orthogonal to this axis. Using *in vitro* preparations of mouse coronal and angled horizontal slices, we previously tested the canonical vs. non-canonical model on the basis of laminar and horizontal conduction velocity. Our results supported a canonical model for the circuits in the slice preparations including AC, by using microstimulation and multi-site recording of planar multielectrode array substrates. In this study, for the next step, by using the similar recording technique, we examined spatial distribution patterns of short term potentiation (for a duration of 10-15 min) induced by local high-frequency stimulation (e.g., 100-Hz short pulses for 1 sec) to mouse AC slices. Each stimulation site on the substrates was selected in the layer 4/5 of AC. The stimulation induced short term potentiation in localized specific sites parallel to the laminar direction from layer 2/3 to 5, and no asymmetry distribution patterns were found. The result is likely to support a canonical model for the circuits in the slice preparations at the spatial resolution (inter-electrode interval=150 μm). These results can provide critical information regarding the extent and spatial patterns of short term plasticity induced by auditory activity in future neural prostheses for AC.

Disclosures: **T. Tateno:** None. **A. Sano:** None.

Poster

596. Auditory Processing: Cortex and Cortical Circuits

Location: Hall A

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Program#/Poster#: 596.10/J23

Topic: D.02. Auditory System

Title: Callosal projections influence neuronal-specific sound-evoked responses in the mouse auditory cortex

Authors: *C. ROCK, A. APICELLA;
Biol., Univ. of Texas San Antonio, San Antonio, TX

Abstract: Auditory information is processed bilaterally in the auditory cortex (AC), and thus interhemispheric communication via the corpus callosum is important for the sound localization processes underlying spatial hearing. However, information is lacking about the specific neuronal microcircuits which are recruited by these callosal projections. A previous study (Kitzes and Doherty, 1994) pairing mono- and binaural sound presentation with electrical stimulation of the contralateral AC showed that three different types of influence are exerted by the callosal projections: suppression, facilitation, or a mixture of both. This assortment of responses is likely due to the heterogenic pool of both pyramidal neurons and interneurons in the AC. In a paper recently published by our lab (Rock and Apicella, 2015) we were able to address this fundamental question of the connectivity patterns of input onto specific neuronal subpopulations in layer 5 of the mouse auditory cortex *in vitro* using optogenetic and electrophysiological methods. We found that callosal projections suppress the activity of corticocortical (CCort) pyramidal neurons, but facilitate firing of corticocollicular (CCol) pyramidal neurons. This difference is mechanistically explained by callosal activation of fast-spiking parvalbumin-expressing interneurons (FS-PARV), which provide selective inhibition to CCort pyramidal neurons. Our results established two distinct previously unknown cortical circuits underlying either callosal suppression (callosal projections → FS-PARV → CCort) or facilitation (callosal projections → CCol) of projecting pyramidal neurons in layer 5 of the AC and attributed a specific function to a genetically defined type of interneuron in interhemispheric communication. In the present study we investigate the preservation of these circuits *in vivo* during sound presentation using extracellular recording and whole-cell patch clamp techniques and optogenetic manipulation of callosal projections and local interneurons in an anesthetized mouse.

Disclosures: **C. Rock:** None. **A. Apicella:** None.

Poster

596. Auditory Processing: Cortex and Cortical Circuits

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Topic: D.02. Auditory System

Support: NSFC Grant 20131351192

Title: Gaba(b) receptors regulate experience-dependent maturation of temporal processing in the primary auditory cortex

Authors: X. LONG[1], R. HAN[2], D. CAI[1], M. LIU[1], Y. ZHENG[1], Y. LIU[1], L. ZHAO[3], J. YAO[1], *K. YUAN[1];
[1]Tsinghua Univ., Beijing, China; [2]Dept. of Otolaryngology, WeiFang Med. Univ., WeiFang, China; [3]Dept. of Otolaryngology, Affiliated Hosp. of WeiFang Med. Univ., WeiFang, China

Abstract: Faithful representation of rapidly successive acoustic signals in the primary auditory cortex (A1) is central to accurate perception of natural sounds such as human speech and animal vocalizations. However, how cortical stimulus-tracking capacity developmentally emerges remains poorly understood. Using *in vivo* whole-cell recordings right after hearing onset, we found that higher inhibition to excitation (I/E) ratio and longer time course of inhibition remarkably weakened the ability of neurons in developing rat A1 to track repeated stimuli. Surprisingly, only five minutes of passive exposure to sounds presented at ethologically high repetition rates reliably improved cortical stimulus-tracking ability. This unexpected plasticity of spike responses resulted from the significant shortening of the duration of inhibitory inputs, which could last for nearly an hour. Further pharmacological experiments revealed that GABAB instead of GABAA receptors took major responsibility for the elongation and rapid plasticity of inhibitory time course in developing cortex. Thus, our results demonstrated hypersensitivity of developing sensory cortex to the temporal feature of successive stimulus events, and suggested that GABAB-medicated, a novel type of plasticity of inhibition plays a critical role in experience-dependent cortical non-map plasticity and maturation of temporal response properties.

Disclosures: **X. Long:** None. **R. Han:** None. **D. Cai:** None. **M. Liu:** None. **Y. Zheng:** None. **Y. Liu:** None. **L. Zhao:** None. **J. Yao:** None. **K. Yuan:** None.

Poster

596. Auditory Processing: Cortex and Cortical Circuits

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Topic: D.02. Auditory System

Support: NIH Grant DC012125

Title: Layer 5 and 6 auditory corticocollicular neurons are differentially distributed with respect to their subcortical targets in the mouse

Authors: *G. YUDINTSEV[1], D. A. LLANO[2];
[1]Neurosci., [2]Mol. and Integrative Physiol., Univ. of Illinois At Urbana-Champaign, Urbana, IL

Abstract: The auditory corticocollicular projection has recently garnered much attention due to its ability to alter response properties of cells in the inferior colliculus. However, the basic anatomical organization of this pathway remains poorly understood. Corticocollicular neurons emanate from two distinct bands of the auditory cortex - layer 5 and deep layer 6 - and differ in their firing properties and cellular morphology. In addition, preliminary results from our laboratory in mouse demonstrate significant heterogeneity in the global distributions of layer 5 and 6 corticocollicular projections, with layer 6 cells spanning a broader region of the auditory cortex, extending more anteriorly and ventrally than layer 5, while layer 5 neurons are more concentrated in the primary auditory cortex, as confirmed by parvalbumin and SMI32 immunoreactivity. To further characterize the differences within the corticocollicular system, we ipsilaterally injected two retrograde tracers Cholera toxin B and Fluorogold into the inferior colliculus and the medial geniculate body, respectively. A subset of layer 5 corticothalamic neurons were also found to project to the inferior colliculus, while layer 6 corticocollicular neurons were found in a band that was distinct from layer 6 corticothalamic neurons. These data extend previous findings that suggest that layer 5 and layer 6 corticocollicular projections have different organizations and, presumably, different roles in modifying inferior colliculus function.

Disclosures: G. Yudintsev: None. **D.A. Llano:** None.

Poster

596. Auditory Processing: Cortex and Cortical Circuits

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Topic: D.02. Auditory System

Support: NIH Grant R21012894

Title: Layer 6 corticothalamic neurons modulate the gain and selectivity of columnar sound processing

Authors: *W. GUO[1,2], A. R. CLAUSE[1,3], A. N. BARTH-MARON[1,4], B. G. SHINN-CUNNINGHAM[2], D. B. POLLEY[1,2,3];
[1]Eaton Peabody Lab., Massachusetts Eye and Ear Infirmary, Boston, MA; [2]Ctr. for Computat. Neurosci. and Neural Technol., Boston Univ., Boston, MA; [3]Dept. Otology and Laryngology, [4]Dept. Neurobio., Harvard Med. Sch., Boston, MA

Abstract: The cortical column is the canonical unit of information processing in the cerebral cortex. Until recently, intermediate layers of processing between the input and output of the column have remained obscure. Here, we explore sensory response modulation imposed by layer 6 (L6) Ntsr1 neurons, which provide the dominant source of corticothalamic projections but also have abundant connections within the local column. We used a cre-dependent viral construct to selectively express channelrhodopsin-2 (ChR2) in L6 auditory cortex neurons (ACtx) of Ntsr1-cre transgenic mice. We then recorded neural responses in the medial geniculate body (MGB) of the thalamus and all layers of ACtx in response to sound stimulation and/or optogenetic activation of Ntsr1 neurons in awake mice under head restraint. Surprisingly, activation of L6 Ntsr1 neurons induced only weak effects on the responsiveness and sensory tuning in downstream MGB neurons. However, photostimulation of Ntsr1 neurons elicited spiking activity in all layers of ACtx. Analysis of local field potentials and current source densities revealed that Ntsr1 neural activation induced a robust gamma oscillation in deep layers (at 100 - 120 Hz) and superficial layers (at 40 - 50 Hz), immediately followed by a low frequency oscillation (1 - 4 Hz) that persisted for hundreds of milliseconds after the cessation of Ntsr1 spiking. These data suggest that L6 Ntsr1 neurons engage distributed networks of excitatory and inhibitory neurons throughout the column that dynamically transform afferent sensory traces depending on the delay between sensory stimulation and Ntsr1 neuron activity. We tested this hypothesis by quantifying changes in gain and selectivity of single unit responses to pure tone stimuli presented at various delays relative to the onset of L6 Ntsr1 neuron activation. Unlike previous reports in visual cortex, L6 Ntsr1 neuron activation induced weak, additive gain to sensory tuning rather than divisive suppression. Intriguingly, the most pronounced changes occurred immediately after the cessation of the activation, where superficial and middle layer neurons exhibited a strong increase in frequency selectivity, followed by an overall gain in response amplitudes. We observed a group of fast-spiking neurons that specifically responded at the offset of laser stimulation, coinciding with the greatest changes in tuning curve gain or selectivity. Overall, these data suggest that L6 Ntsr1 neurons modulate columnar sound processing in ACtx via local inhibitory circuits, and the direction and strength of the effects critically depend on the relative timing between L6 Ntsr1 neuronal activity and sensory stimuli.

Disclosures: W. Guo: None. **A.R. Clause:** None. **A.N. Barth-Maron:** None. **B.G. Shinn-Cunningham:** None. **D.B. Polley:** None.

Poster

596. Auditory Processing: Cortex and Cortical Circuits

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Support: NIH Grant DC012125

Title: Computational studies of a thalamocortical network containing the thalamic reticular nucleus, using a novel mutual information estimator to measure network performance

Authors: *E. GRIBKOVA, D. A. LLANO;
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Abstract: The dynamics of neural networks that involve thalamocortical (TC) neurons and the thalamic reticular nucleus (TRN) remain vaguely understood. Bursting, a characteristic mode of firing in the thalamus, is observed during some of these events and is primarily influenced by calcium T-currents in TC cells. Applying a Hodgkin-Huxley model framework, consisting of a TC neuron, TRN neuron, external inputs to the TC and TRN cells, and a layer 4 (L4) thalamorecipient neuron, we study bursting in open-loop circuits in this TRN-TC-L4 network with the analysis of T-current variations in the TC cell and how they affect signal transmission from TC to L4. Using a mutual information estimator with an adaptive partition for signals with different time scales, we show that the time constants of the synaptic input to the TC cell, and of the TC to L4 synapse, as well as TC cell calcium T-current conductance all influence mutual information between the input to the TC cell and L4 spiking. In particular, a TC calcium T-current conductance of at least 40 nS is required to enhance the response of the L4 cell to high frequency input at the TC cell, while both synaptic time constants appear to have optimal values of at least 25 ms at which maximal enhancement of the L4 response is observed. These studies suggest that the TRN can enhance mutual information between sensory input to the thalamus and cortical responses, and that mutual information is sensitive to the time constants of both thalamocortical synapses and the external input to the thalamus.

Disclosures: **E. Gribkova:** None. **D.A. Llano:** None.

Poster

596. Auditory Processing: Cortex and Cortical Circuits

Location: Hall A

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NIH Grant R01EY019049

Title: Auditory cortex controls sound driven innate defense behavior through corticofugal projections to inferior colliculus

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Abstract: Defense against environmental threats is essential for animal survival. However, the neural circuits responsible for transforming unconditioned sensory stimuli and generating defensive behaviors remain largely unclear. Here, we show that corticofugal neurons in the auditory cortex (ACx) targeting the inferior colliculus (IC) mediate an innate, sound-induced flight behavior. Optogenetic activation of these neurons, or their projections in the IC, is sufficient for initiating flight responses, while inhibition of these projections reduces sound-induced flight responses. Corticocollicular axons monosynaptically innervate neurons in the cortex of the IC (ICx), and optogenetic activation of projections from the ICx to the dorsal periaqueductal gray is sufficient for provoking flight behaviors. Our results suggest that ACx can both amplify innate acoustic-motor responses and directly drive flight behaviors in the absence of sound input through corticocollicular projections to ICx. Such corticofugal control may be a general feature of innate defense circuits across sensory modalities.

Disclosures: X.R. Xiong: None. **F. Liang:** None. **B. Zingg:** None. **X. Ji:** None. **L.A. Ibrahim:** None. **H.W. Tao:** None. **L.I. Zhang:** None.

Poster

596. Auditory Processing: Cortex and Cortical Circuits

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Support: GACR P303/14/28334S

GACR P303/12/1347

Title: Divergent intrinsic electric properties of L5 pyramidal neurons in the primary auditory cortex and auditory belt of rat

Authors: *O. PROFANT[1,3], K. PYSANENKO[1], M. KRALIKOVA[1], J. SYKA[1], L. VALIHRACH[4], M. ANDEROVA[2], R. TURECEK[1];
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Abstract: The auditory cortex (AC) receives the majority of auditory afferent inputs. It is comprised of the primary (A1), secondary and tertiary (belt) regions. Our previous work indicated differences between the sound-evoked spiking patterns of A1 and belt neurons, raising the question as to what extent are incoming sensory signals processed differently by neurons in these two parts. In this study, we investigated the intrinsic electrical properties of layer 5 pyramidal neurons (PNs) in acute AC slices isolated from 30-35-day-old rats. Regular-spiking (RS) cells predominated amongst the PNs in both AC areas. Interestingly, RS cells from A1 showed significantly higher excitability at rest. Their time membrane constants and input resistances were significantly increased compared to those found in RS cells from the belt region. Accordingly, A1 PNs generated action potentials with shorter latencies and lower rheobases. This suggests that A1 and belt neurons could differ in the presence of currents constitutively activated at resting membrane potential (~ -77 mV). We observed Kleak, inwardly-rectifying K+ (IRK) and hyperpolarization/cyclic nucleotide gated cation (HCN) channels participating at resting membrane conductance in AC PNs. No significant differences in amplitudes of Kleak or IRK mediated currents were observed between A1 and belt neurons. In contrast, the densities of HCN-mediated currents (Ih) were nearly doubled in neurons of the belt region compared to those from A1. Single-cell RT-qPCR analysis revealed the prevalence of HCN1and HCN2 mRNAs and minor contributions of HCN3-4 transcripts in both auditory areas. Experimental blockade of Ih hyperpolarized PNs (-2.7 mV vs -4.2 mV for A1 vs belt PNs) and increased their input resistances, suggesting Ih to be the major factor regulating the excitability of belt neurons at rest. Furthermore, Ih generated a depolarization sag in the voltage responses to hyperpolarizing current steps injected into PNs. The activation kinetics of the sag was fast enough to shorten the duration of the after-hyperpolarization phase of action potentials in the belt neurons. Consistently, the jitter of steady-state action potentials evoked by repetitive current stimuli was significantly reduced in belt PNs compared to their A1 counterparts. This suggests that Ih could help to maintain the persistent firing of neurons from the belt region. Our data supports the view that the *in vivo* observed diversity in spiking patterns of A1 and belt neurons could be at least partially explained by differences in their intrinsic electrical properties.

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Poster

596. Auditory Processing: Cortex and Cortical Circuits

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Title: Congenital deafness leads to increased cortical thickness in auditory association cortex and Broca's area

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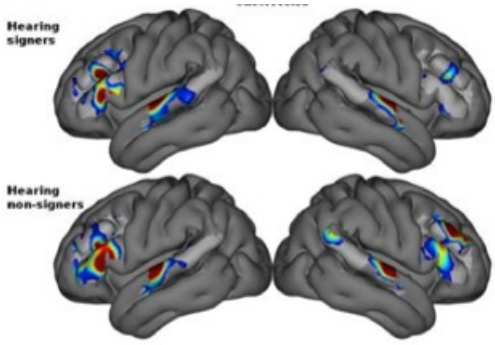
Abstract: Sensory deprivation since birth leads to a variety of structural and physiological brain alterations. This is true for both congenital blindness and congenital deafness, although at different degrees. Several studies have indicated major changes in white matter volume and tracts as measured by diffusion techniques and also in the grey matter occurring outside auditory areas. There are however major discrepancies in the literature concerning those parts of the brain that are modified by hearing loss. In our study, we have concentrated our analysis on auditory and language areas in a large sample of congenitally deaf (CD) individuals who never used hearing aids and were proficient in sign language. They were compared to two groups of hearing subjects, one who acquired sign language (HS) and one who did not (HNS). We analyzed cortical thickness from whole brain MR images with well-defined regions of interests into secondary auditory areas and Broca's area. Our results showed an increased cortical thickness in

Broadmann's area 21 and 22 (secondary auditory cortex) and 44 and 45 (Broca's area) in CD. HS showed also a trend in an increased cortical thickness in language areas compared to HNS. Our results indicate that contrary to congenital blindness, the primary auditory area in congenital deafness does not undergo the same plastic changes.



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Poster

597. Interactions between Auditory and Non-Auditory Modalities

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Topic: D.03. Multisensory Systems

Support: JS McDonnell Collaborative Research Grant 220020255

Title: Differential effects of auditory and visual alpha power in relation to concomitant haemodynamic response

Authors: ***G. Y. BEZGIN**[1], T. BROWN[2], Z. FATIMA[2], A. R. MCINTOSH[2];
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Abstract: Sensory-related alpha activity (7-12 Hz) in early auditory and visual cortices has been a subject of debate. Even more obscure and contradictory is available evidence on relation between sensory alpha activity and blood oxygenation metabolism as measured by functional magnetic resonance imaging (fMRI). We addressed both issues with simultaneously acquired electroencephalography (EEG) and fMRI data under an audiovisual reaction time task. Alpha, as well as beta (16-30 Hz) and gamma (32-100 Hz) band powers were assessed in two ways: 1)

overall band power in 1s pre- and 2s post-stimulus epochs, and 2) 1s post- minus 1s pre-stimulus power content. These metrics were correlated across trials with fMRI signal change, involving subtle stimulus-related fluctuations of the latter. Furthermore, these data were also correlated with stimulus response reaction time, as well as EEG signal complexity measured by multiscale entropy (MSE), involving both electrode-based and source-localised EEG activity, wherein the sources were informed by fMRI contrasts. We observed similarities and distinctions between auditory and visual modalities across applied metrics: both exhibited high and significant correlations between all three band powers (alpha in particular: correlation coefficient ranged from 0.76 to 0.96, $p<0.0001$ for all region pairs). The effects of reaction time and response accuracy on band powers were more pronounced in the auditory modality (average increase from $r=0.14$ for inaccurate trials to $r=0.37$ for accurate trials, $p<0.0001$). Visual alpha was systematically suppressed instantaneously after a correct stimulus response (correlation between overall power and post-stimulus modulation: $r=-0.4$, $p<0.001$). Significant correlations between subtle blood-oxygen level dependent (BOLD) fluctuations and stimulus-locked alpha-power were observed in both auditory ($r=0.32$, $p<0.0001$) and visual ($r=0.2$, $p<0.0001$) modalities. MSE was significantly correlated with beta power (visual: $r=0.45$; auditory: $r=0.38$). Overall, this study assesses the relation between fMRI and alpha power in the early auditory cortex and its visual counterpart, exploring effects of response accuracy and lateralisation. Importantly, it emphasises the advantage of using a combined EEG-fMRI setup in conjunction with a simple multisensory perception paradigm, assessed trial by trial - and thus offers a novel paradigm for multimodal experiments acquired with simultaneously combined neuroimaging techniques.

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Poster

597. Interactions between Auditory and Non-Auditory Modalities

Location: Hall A

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Topic: D.03. Multisensory Systems

Title: McGurk illusion recalibrates neural representation and perception of subsequent auditory input

Authors: ***C. S. LÜTTKE**, M. EKMAN, M. A. J. VAN GERVEN, F. P. DE LANGE; Donders Inst. Brain, Cognition and Behaviour, Nijmegen, Netherlands

Abstract: Observing the mouth of a speaker helps interpreting the auditory signal in a conversation, especially in noisy conditions. Not only does visual input help in interpreting

audiovisual signals, it can also determine how the brain interprets subsequent ambiguous auditory information. Here we examined the influence of McGurk stimuli (where an unambiguous auditory /aba/ and an unambiguous visual /aga/ are merged to the percept of /ada/) on subsequent unambiguous auditory input. In a combined behavioral and fMRI experiment, participants categorized auditory and audiovisual speech stimuli (as /aba/, /ada/ or /aga/). Participants were preselected on the basis of their proneness to the McGurk illusion (on average, >82% illusions). Interestingly, following a McGurk stimulus (during which an auditory /aba/ input, combined with a visual /aga/ input, is interpreted as /ada/), an auditory /aba/ in isolation was more often interpreted as /ada/ (from 16% to 27%, p=0.0009). This effect could not be explained by simple priming effects, as auditory /ada/ in isolation did not influence the interpretation of a subsequent auditory /aba/ (18% vs. 16%, p=0.85). Moreover, perception of auditory /ada/ and /aga/ were unaffected by previous McGurk trials. This phonetic recalibration was also reflected in the auditory cortex. We trained a classifier to distinguish the neural representation of /aba/ and /ada/ in auditory cortex on a separate data set. When the auditory input /aba/ was perceived as /ada/, the classifier categorized the neural activity elicited by the stimulus more often as /ada/. Our results suggest that after experiencing the McGurk effect, the brain may shift the neural representation of an /aba/ sound towards /ada/, culminating in a change in perception of subsequent auditory /aba/ input towards previous perception.

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Poster

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Title: Is the sound-induced double-flash illusion generated in primary visual cortex? Insights into multisensory integration from intracranial EEG recording in humans

Authors: *E. M. YEAGLE[1,2], P. MEGEVAND[3], M. MERCIER[4,5], M. T. KAUFMAN[6], L. CHARTARIFSKY[6], A. K. CHURCHLAND[6], A. D. MEHTA[1,2];
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Abstract: A hallmark of cognition is the ability to assemble information from diverse sources, and to use the outcome to guide complex behavior. Here, we leverage a multisensory illusion paradigm to investigate the neural circuits underlying the assembly of information from visual and auditory modalities. In the sound-induced double flash illusion, judgments about a visual flash are influenced in a time-dependent way by auditory beeps. A single flash presented with two beeps often leads to the perception of a second flash, but only when the beeps are close together. Prior fMRI and extracranial EEG studies have localized correlates of this illusion to occipital cortex, but the illusion has not been studied in humans using intracranial recordings. We examined neural responses in this paradigm in three patients with intractable epilepsy, who had been implanted with intracranial electrodes covering occipital cortex in preparation for surgery to treat their seizures. To induce the illusion, subjects were presented with a single flash (16.67 ms) paired with two beeps. The first beep was simultaneous with the flash, while the second occurred after a variable interval (stimulus-onset asynchrony, SOA) of 50-500 ms. Control conditions presented single or double flashes without sound, a single flash paired with a concurrent beep, and a double flash paired with two concurrent beeps. Subjects identified each trial as presenting a single or double flash. As reported for healthy controls, our patients integrated the two modalities: they were more accurate for conditions with concordant visual and auditory stimuli than for visual-only conditions, they perceived the illusion, and they perceived the illusion more often for short SOA trials than for long SOA trials. For neural analysis, we selected the SOA for each subject that most closely produced 50% accuracy. We then compared neural responses on trials when the subject perceived the illusion (reported 2 flashes) to trials when they did not (reported 1 flash). We focused our analysis on early visual cortex. In contrast with earlier findings, we identified no significant difference between illusion and non-illusion trials in early visual cortex, in either the event-related potential or high-gamma power (65-175 Hz). However, preliminary findings suggest that a neural signature of the illusory flash may be present in extrastriate or later visual areas. These recordings may therefore offer greater resolution of the brain areas involved in multisensory integration, pointing to later stages of visual processing than previously believed.

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Poster

597. Interactions between Auditory and Non-Auditory Modalities

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Topic: D.03. Multisensory Systems

Support: ERC 249425 "CriticalBrainChanges"

Title: Multisensory learning through passive audio-visual stimulation in six month old infants

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Abstract: The developing brain needs to adapt to the statistical properties of the sensory environment; the detection, binding, and recognition of new sensory information from different modalities is influenced by the likelihood of specific crossmodal combinations. We investigated multisensory learning in infants on a neural level through passive exposure of audio-visual combinations with different probabilities. While recording the EEG six month old infants were presented with two frequently occurring audio-visual standard combinations (70 %) and infrequently occurring audio-visual deviant stimuli. The latter comprised (1) new combinations of the auditory and visual stimuli comprising the standard stimuli (20 %) and (2) an audio-visual combination of new auditory and new visual stimuli (10 %). We expected that infants would learn the frequent standard combinations and expected a deviant response in the event-related potentials (ERPs) for both newly combined as well as new audio-visual stimuli. Results showed a long-lasting ERP deviant response to new audio-visual (200 - 1000 ms) and, importantly, an ERP deviant response to infrequent audio-visual stimulus combinations as well, however with a longer latency (420 -1000 ms). By contrast, a similar effect was found in adults only if audio-visual combinations were task relevant but not under passive exposure. Thus, the present study demonstrates a higher sensitivity of infants for crossmodal environmental statistics as had previous been shown for individual sensory systems.

Disclosures: S. Rohlf: None. **B. Habets:** None. **B. Roeder:** None.

Poster

597. Interactions between Auditory and Non-Auditory Modalities

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Topic: D.03. Multisensory Systems

Title: Cross-modal processing in the auditory and visual cortex: fNIRS study with a double-flash illusion

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Abstract: [Purpose] Hearing and sight are the five human important senses and a brain finally processes these information derived from the senses. In everyday life, information of hearing and sight is not processed separately but is processed interactively. Thus, to clarify the mechanism of sensory information processing, details of cross-modal interactions of hearing and sight should be considered. Auditory and visual interaction is measured using fNIRS(functional Near Infrared Spectroscopy). [Method] Information of behavior and brain functions with a double-flash illusion is analyzed. As the block design, the following three types of stimuli are prepared. We used the block design that has three tasks. Each task has different number of flashes. First task has one flash and two beeps. Second task has one flash and one beep. Last task has two flashes and two beeps. In the task, we applied ten same type of stimuli. In the experiment, fNIRS facility that was manufactured by Hitachi medical was used and cerebral blood flow in the whole brain was measured. The subjects were thirteen healthy adults and they were 22-24 years old. [Results] According to t-test($p<.05$), we measured a number of times in perception of visual stimuli. In this result, the subjects were divided into three groups. One group was defined as the group in which the subjects strongly got illusory impression. Another was defined as the group in which the subjects got weakly illusory impression. The other was defined as the group in which the subjects didn't get an illusory impression. We tested whether a change of cerebral blood flow in a task was very different from in a rest. If a change in cerebral blood flow in a task had been significantly different from in a rest, it was decided that part of brain was active. The subjects who strongly got illusory impression had some active areas of Superior Temporal Sulcus and Intraparietal Sulcus. We hypothesized that a subject got illusory impression to resolve the conflict of auditory and visual information. We tested whether the hypothesis was true or not. The subjects who strongly got illusory impression had some active areas of Superior Temporal Sulcus, which was an integration site, and Intraparietal Sulcus, which was an integration site of somatic and visual sensation. As the result, it was suggested that Intraparietal Sulcus might have a function of the integration site of auditory and visual sensation.

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Poster

597. Interactions between Auditory and Non-Auditory Modalities

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Support: Grant-in-Aid for Scientific Research, JSPS (25245069)

Grant-in-Aid for Scientific Research, JSPS (26285160)

Title: Audio-visual integration for motion perception

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Abstract: The alternation of sound location induces illusory visual motion when vision cannot provide accurate spatial information. A visual stimulus blinking at a fixed location was perceived to be moving laterally when the flash onset was synchronized to an alternating left-right sound source. This illusory visual motion was strengthened with an increasing retinal eccentricity and occurred more frequently when the onsets of the audio and visual stimuli were synchronized. We investigated brain activity for the sound-induced illusory visual motion with a 7T fMRI. Strong activation was observed in hMT when subjects viewed apparent motion stimuli, but not when they viewed the stimulus blinking at a fixed location. However, the activation was also observed for the stimulus blinking at the fixed location when the flash onset was synchronized to an alternating left-right sound source. These results indicate that the hMT is responsible for the audio-visual integration for motion perception.

Disclosures: T. Omi: None. **W. Teramoto:** None. **S. Higuchi:** None. **S. Hidaka:** None. **Y. Sugita:** None.

Poster

597. Interactions between Auditory and Non-Auditory Modalities

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Doris Duke Charitable Foundation Grant 2012062 (PET)

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Title: Audiovisual speech perception and presence of the McGurk effect in left-hemisphere stroke patients and matched control participants

Authors: *L. C. ERICKSON[1], M. E. FAMA[1], K. A. SPIEGEL[1], E. H. LACEY[1], L. M. SKIPPER-KALLAL[1], S. XING[1], J. P. RAUSCHECKER[1], P. E. TURKELTAUB[1,2]; [1]Georgetown Univ. Med. Ctr., Washington, DC; [2]Res. Div., MedStar Natl. Rehabil. Hosp., Washington, DC

Abstract: Introduction: The McGurk effect is a behavioral measure of audiovisual (AV) speech integration, where the observation of incongruent auditory and visual speech can lead to a percept that is different from either input signal (McGurk and MacDonald, 1976). It is unclear how left-hemisphere (LH) damage impacts AV speech processes. In this study, we examined whether AV speech perception was altered in 34 people with LH strokes compared to 27 matched controls, as tested by the McGurk paradigm. Methods: An adapted McGurk paradigm was created to accommodate language impairments in stroke patients. Stimuli consisted of whole words ("key", "tea", "pea"), and three response options were presented as pictures and written words ("key", "tea", "pea"). For congruent trials, the sound and video matched. For incongruent trials, the "key" video was presented with the auditory "pea" and had 7 timing offsets binned into three types: auditory lead (AL), middle range (MID), and visual lead (VL). For these trials, responses corresponded to the "key" visual input (keyVIS), the "pea" auditory input (peaAUD), and the McGurk "tea" percept (teaMcG). Stroke participants were included if they had a LH stroke at least 6 months prior to the study, no significant brain damage outside the LH, and >80% accuracy on congruent trials. The behavioral analysis included 34 LH stroke patients (age: 59.6 ± 10.6; 10 females; 30 right-handed) and 27 control participants (age: 59.4 ± 13.8; 18 females; 24 right-handed). Results: There were no significant between-group differences or interactions for AL trials (keyVIS: 23.6% stroke vs. 26.4% control; teaMcG: 34.7% stroke vs. 36.2% control; peaAUD: 41.8% stroke vs. 37.4% control) or MID trials (keyVIS: 29.8% stroke vs. 31.7% control; teaMcG: 53.0% stroke vs. 63.0% control; peaAUD: 17.2% stroke vs. 5.3% control). For VL trials, stroke participants reported peaAUD more than controls (p=0.001; 21.8% stroke vs. 5.3% control); however, there were no differences for keyVIS (27.4% stroke vs. 34.6% control) or teaMcG (50.8% stroke vs. 60.1% control). Conclusions: In this preliminary between-group comparison, stroke patients and control participants demonstrated similar patterns of responses to McGurk stimuli. However, when the visual signal was presented first, stroke patients reported

the auditory percept more than controls. We suggest that since the current stroke group has heterogeneous LH damage, it is possible some regions necessary for AV speech integration may be intact in some subjects. Thus, the next stage of analyses will examine individual differences that may relate to AV integration in this task, such as lesion size and location.

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Poster

597. Interactions between Auditory and Non-Auditory Modalities

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Title: The auditory cortex tracks the temporal dynamics of visual speech during silent lip-reading

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Abstract: Human speech is multisensory by nature: our lips, face and body are set into action when we speak; and being able to see our interlocutor complements and enriches our understanding of what is being said. How does visual speech affect the auditory cortex? According to an influential hypothesis, visual speech could induce phase reset of oscillatory activity in auditory cortex, thus modulating its excitability and optimizing the decoding of auditory speech (Schroeder et al., Trends Cogn Sci 2008). To explore this hypothesis, we recorded the responses of human cerebral cortex to naturalistic auditory and visual speech through intracranial EEG electrodes in patients with drug-resistant epilepsy. Electrodes were

localized by co-registering pre- and post-implantation high-resolution MRI and CT scans. Participants watched and heard short (8-12 second) stories whose ending was cut off; after each story, they indicated whether a written word provided an appropriate ending. Each story was repeated several times, allowing us to measure the degree of phase-locking of the intracranial EEG across repeats of the same story (intertrial coherence, ITC) through time-frequency analysis. We defined auditory cortex as those electrodes that showed increased high-gamma power as well as delta- and theta-band phase-locking to auditory speech. We found that auditory cortex displayed significant phase-locking to visual speech (silent lip-reading) between 1 and 5 Hz, without any concomitant increase in power at these frequencies. We also observed a slight increase in high-gamma power. We then cross-correlated the ITC with mouth opening (approximated by the envelope of the auditory speech signal) and found positive correlations at the same frequencies, indicating that phase-locking in auditory cortex reflected specific characteristics of the visual speech signals. We also found a positive correlation between behavioral performance during silent lip-reading and the 1-to-5-Hz ITC to visual speech in auditory cortex. In order to examine how visual speech signals influence the processing of auditory speech, we compared the amount of phase-locking in auditory cortex when perceiving audiovisual vs. auditory speech and found higher phase-locking to audiovisual speech at 4 and 5 Hz. Our results indicate that oscillatory activity in auditory cortex reflects the slow dynamics of visual speech during silent lip-reading. They support the notion that visual speech gestures influence the oscillations, and hence the response of auditory cortex to speech sounds. More generally, they underscore the possible role of neuronal oscillations in multisensory integration and predictive coding.

Disclosures: **P. Megevand:** None. **M.R. Mercier:** None. **D.M. Groppe:** None. **C.E. Schroeder:** None. **N. Mesgarani:** None. **A.D. Mehta:** None.

Poster

597. Interactions between Auditory and Non-Auditory Modalities

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 597.09/J39

Topic: D.03. Multisensory Systems

Support: Higher Education Authority Ireland: Programme for Research in Third-Level Institutions and co-funded under the European Regional Development fund.

Title: Eye can hear clearly now: visual speech increases the sensitivity of auditory cortex to peri-threshold speech-in-noise

Authors: *E. C. LALOR, M. J. CROSSE;
Trinity Col. Dublin, Dublin, Ireland

Abstract: It is well established that viewing a speakers' articulatory movements can improve comprehension of auditory speech, especially in noisy environments (Sumby and Pollack, 1954). It has been suggested that this effect is underpinned by an early integration mechanism where visual speech information increases the sensitivity of auditory cortex to acoustic information and a late integration stage that constrains the possible candidates in a spoken utterance based on visual information about a speaker's articulators (Peelle and Sommers, 2015). Evidence for the early integration mechanism comes from research showing that viewing a speaker's face enhances low frequency cortical entrainment to the speech envelope in auditory cortex (Zion-Golumbic et al., 2013). While this has been shown for the case of a single speaker in quiet and the case of an attended speaker in a two-speaker environment, it has not been shown for the case where the audio speech is degraded by noise to the point of being unintelligible. This is important as the cortical representation of the speech envelope has been shown to be relatively insensitive to background noise for intelligible speech, but to be much reduced when speech become unintelligible (Ding & Simon, 2013). In this study, we examined the impact of visual speech on envelope entrainment for clean speech and speech-in-noise using electroencephalography (EEG). Stimuli consisted of audio-only (A), visual-only (V) and audiovisual (AV) continuous speech segments of ~60 s duration. For speech-in-noise, the audio was embedded in spectrally matched white noise at an SNR of −9 dB, a level where individual words could occasionally be discerned but where the semantic content was essentially unavailable. Word detection and self-reported intelligibility scores were significantly improved in the AV condition relative to the A condition. While only very low levels of cortical entrainment to the envelope were evident for auditory cortex in the A and V conditions, a substantial index of envelope tracking was apparent for the AV condition. These results suggest that, at SNRs where speech is largely unintelligible and cortical entrainment much diminished relative to clean speech, the addition of visual speech information improves speech comprehension by facilitating a dramatic increase in the sensitivity of auditory cortex to the acoustic speech information.

Disclosures: E.C. Lalor: None. **M.J. Crosse:** None.

Poster

597. Interactions between Auditory and Non-Auditory Modalities

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 597.10/J40

Topic: D.03. Multisensory Systems

Support: Swiss National Fund 320030_149319

Title: A computational model of content-specific and content-free cross-modal predictions in audiovisual speech

Authors: *I. OLASAGASTI, S. HOVSEPYAN, S. BOUTON, A.-L. GIRAUD;
Dept. of Basic Neurosci., Univ. of Geneva, Geneve, Switzerland

Abstract: Speech processing is inherently multisensory and hierarchical, allowing one sensory system to use predictions about timing and content from the other one to facilitate parsing and decoding. To explore the role of predictions in speech processing, we developed a computational predictive coding model of audiovisual speech integration for the recognition of syllables. Congruent and incongruent audiovisual stimuli (McGurk stimuli) constitute a useful behavioral and electrophysiological model to investigate the mechanisms of audiovisual speech integration. Our model focuses on explaining two basic findings from the electrophysiological literature: that visual stimuli affect brain activity in early auditory cortex in a content unspecific way, and in a content-specific way in higher cortical areas (e.g. Arnal et al., 2009; Hertrich et al., 2009). We modeled audiovisual speech processing using a hierarchical Bayesian inference model in which recognition arises from top-down predictions and bottom-up prediction errors. The model includes amodal recognition units representing individual /aCa/ speech tokens at the top of the model hierarchy (C being a stop consonant). Each unit generates predictions about audiovisual sensory features consistent with the token it represents. The visual stimulus was characterized by lip aperture and the acoustic stimulus by two sensory features: the second formant transitions and voicing. In addition, the units generated predictions about sensory features at two distinct temporal scales broadly related to the syllabic and phonemic levels. Cross-modal predictions included speech-specific information driven by the correlation of lip closure, place of articulation and second formant transitions distinguishing between voiced /aba/, /ada/ and /aga/ (or unvoiced /apa/, /ata/ and /aka/). Cross-modal content-unspecific predictions were driven by the correlation between lip motion and the acoustic speech envelope. This model provides a novel cross-modal predictive coding interpretation of audiovisual integration and specifies two potential ways through which visual information affects speech processing: 1) content-specific information such as place of articulation favors specific speech tokens and their related recognition units, and 2) content unspecific timing information aligns internal rhythms and helps the parsing of continuous speech. The model thus provides a unified account of ‘what’ and ‘when’ predictions across modalities, assigning a specific role to distinct time scales in a well-established model of early audiovisual integration.

Disclosures: I. Olasagasti: None. **S. Hovsepyan:** None. **S. Bouton:** None. **A. Giraud:** None.

Poster

597. Interactions between Auditory and Non-Auditory Modalities

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 597.11/J41

Topic: D.03. Multisensory Systems

Title: Auditory and tactile processing and links to autism spectrum disorder symptoms

Authors: *L. K. BRYANT[1], M. T. WALLACE[1], C. J. CASCIO[2];
[2]Psychiatry, [1]Vanderbilt Univ., Nashville, TN

Abstract: Differences in response to sensory input have long been observed in individuals with autism spectrum disorder (ASD) and are now included among the clinical diagnostic criteria for ASD. Atypical sensory responsiveness manifests itself on a continuum spanning hypo-responsive and hyper-responsive patterns of behavior. It is possible that such altered sensory responsiveness is related to the processing and interpretation of sensory signal strength. However, sensory responsiveness to basic stimulus properties such as intensity has seldom been studied in a manner that allows a complete characterization of the full dynamic response range. Such a characterization would represent an invaluable foundation upon which ASD research could be conducted. We examined auditory and tactile responsiveness to varying levels of stimulus intensity in neurotypical adults using a detection task. A subset of these participants had first-degree relatives with an autism spectrum disorder diagnosis. ASD is highly heritable, and previous studies suggest that siblings of individuals with ASD also exhibit behavioral hypo- and hyper-responsiveness to sensory input. Our preliminary results suggest participants with a first-degree relative with an autism spectrum disorder demonstrate altered auditory and tactile detection thresholds, increased variability in response patterns, and a wider dynamic detection range. Ongoing work includes the correlation of these psychophysical data with self-report data on sensory responsiveness and subclinical autism symptoms, assessment of performance in response to paired audiotactile stimuli, and task adaptation to examine neural signatures of differential auditory and tactile processing using fMRI and EEG methods. This work holds great promise in laying the necessary foundation for studies directed toward better characterizing differences in sensory and multisensory function in autism.

Disclosures: L.K. Bryant: None. **M.T. Wallace:** None. **C.J. Cascio:** None.

Poster

597. Interactions between Auditory and Non-Auditory Modalities

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 597.12/J42

Topic: D.03. Multisensory Systems

Title: Does sound localization improve with obstructed somatosensory feedback?

Authors: *N. SAVIJA[1], P. DI NOTA[2], G. R. LEVKOV[3], G. A. ESCOBAR[1], K. SMITH[3], J. F. X. DESOUZA[4];
[2]Dept. of Psychology, [3]Dept. of Biol., [4]Ctr. for Vision Res., [1]York Univ., Toronto, ON, Canada

Abstract: This study examines neural integration of the sensory modalities of vision and hearing. The objective is to investigate whether an effect of cross-modal compensation of visual to auditory networks in human participants occurs with the removal of visual input. Using opaque contact lenses, visual input was obstructed during a sound localization task over 8 hours. Individuals were placed in a sound attenuated room, in the centre of a semi-circle consisting of 16 equally distributed speakers. Participants were required to localize sound, and actual and perceived sound locations were recorded at 7 time points across 5 hours. With the absence of somatosensory feedback on the face (i.e. opaque contact lenses versus using a blindfold), this study obtained a model for true blindness. Each participant was exposed to tactile, auditory, and gustatory stimuli. Using a difference score between the actual and perceived speaker location, sound localization was investigated. In the interest of investigating an improvement across time, an analysis of centric and eccentric speaker locations was completed. When speakers were grouped in to four quadrants; (1) left 135-180°, (2) fronto-left 90-135°, (3) fronto-right 45-90°, and (4) right 0-45°, there was a significant main effect of centricity, with participants performing significantly worse on right quadrant trials when compared to fronto-left and fronto-right trials. Additionally, a significant interaction between session and centricity revealed that when looking at each session individually, participants performed worse in quadrant 4 when compared to quadrants 2 and 3, but not compared to quadrant 1, in all sessions except session 4 (after 90 mins of blindness). The preliminary analysis of this study did not exhibit an overall improvement in error reduction for sound localization across time in visually deprived participants. It is possible that the lack of visual calibration (the association of location in space with source of sound), may impact the interaural time and intensity differences, and thus not result in overall reduction of errors across time, particularly in speakers located in the far left and right quadrants, as seen in this study. Although there was no improvement overall across time **for the preliminary results**, the significant main effect of speaker and centricity does not rule out a cross-compensation model for auditory and visual networks **and requires further analysis of the data.**

Disclosures: N. Savija: None. **P. Di Nota:** None. **G.R. Levkov:** None. **G.A. Escobar:** None. **K. Smith:** None. **J.F.X. DeSouza:** None.

Poster

597. Interactions between Auditory and Non-Auditory Modalities

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 597.13/J43

Topic: D.03. Multisensory Systems

Support: NSERC 346135-2012

Title: The multisensory integration of naturalistic musical stimuli

Authors: *M. P. OLSHANSKY[1,3], J. F. X. DESOUZA[1,3,2];
[1]Psychology, [2]Biol., York Univ., Toronto, ON, Canada; [3]Ctr. for Vision Res., Toronto, ON, Canada

Abstract: Multisensory integration is a critical perceptual mechanism, aiding our ability to accurately respond to events in our environment. What has not been examined is the role of attention as well as experience in modulating the multisensory integration of naturalistic stimulus. In the first of two experiments, functional magnetic resonance imaging (fMRI) data was collected from 11 participants in order to investigate the effects of attentional modulation in unisensory (i.e., auditory and visual) and multisensory (i.e., audiovisual) stimuli with a task that directed participants' attention to either auditory or visual features of complex naturalistic stimuli (four acoustic guitar vignettes, 6 seconds each). During unisensory events, our results indicate widespread increases in neural activity during both visual and auditory attention in several cortical regions when compared to passive stimulus presentation. During multisensory events, focused attention to auditory features resulted in significantly more activity in the frontal and parietal regions compared to passive viewing; whereas focused attention to visual features additionally activated the bilateral caudate, insular cortex, and the left thalamus. Building on previous findings (Pynn & DeSouza, 2010), in a comparison between multisensory and unisensory attention, our results reveal significantly greater multisensory enhancement in a frontoparietal network, including regions which are known to processes both attention and multimodal cues. Our results reveal a distributed network of nodes spanning from the parietal lobules to the frontal cortex, which are modulated more strongly by attention during multisensory processing as compared to unisensory processing. In order to assess the effects of expertise on the multisensory integration of naturalistic musical stimuli, our second experiment investigates the effects of musical experience on multisensory integration in a similar paradigm to experiment #1. 22 participants (11 musicians, 11 non-musicians) performed a 2 alternative forced choice task where participants were required to determine which of two brief audio, video, or audiovisual vignettes depicting musical notes being played on a guitar was a higher

pitch. Our preliminary results indicate that unimodal cues were equally reliable for both groups, and visual cues were most reliable for both musicians and non-musicians ($p < 0.05$; both groups) after controlling for task difficulty. Our experiments are some of the first to use naturalistic musical stimuli to investigate the role of endogenous attention and musical experience on multisensory integration.

Disclosures: **M.P. Olshansky:** None. **J.F.X. DeSouza:** None.

Poster

597. Interactions between Auditory and Non-Auditory Modalities

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 597.14/J44

Topic: D.03. Multisensory Systems

Support: NSF Grant 1329255

Title: Visual activation of auditory field maps across Heschl's Gyrus and surrounding cortex

Authors: *B. BARTON, J. H. VENEZIA, K. SABERI, G. HICKOK, A. A. BREWER;
Univ. of California, Irvine, Irvine, CA

Abstract: A primary organizing principle of visual cortical organization is the visual field map (VFM): neurons with visual receptive fields next to one another in visual space are located next to one another in cortex, forming one complete representation of visual space. Similarly, we have shown that auditory cortex is organized into auditory field maps (AFMs): neurons with auditory receptive fields that prefer a unique combination of spectral and temporal acoustic dimensions lie next to similarly specialized neurons. Here we investigate the cross-sensory activation of visual field mapping stimuli within AFMs in the vicinity of Heschl's Gyrus (HG). FMRI and a sparse-sampled traveling wave paradigm measuring tonotopic and periodotopic gradients were used to identify AFMs in four human subjects. Similarly, FMRI and population receptive field (pRF) modeling, standard methods for identifying VFMs, were used to identify visual activation within AFMs within these same subjects. Our results show that 1) there are AFMs within the cortical region surrounding HG and 2) that visual activation extends from the HG maps into these surrounding regions. This pattern of cross-sensory activation of primary and early auditory cortex by simple checkerboard visual stimuli resembles similar patterns of cross-activation in macaque measurements. In addition, this cross-sensory activation in normal subjects might be the basis for the visual reorganization of auditory cortex in congenitally deaf subjects.

Disclosures: **B. Barton:** None. **J.H. Venezia:** None. **K. Saberi:** None. **G. Hickok:** None. **A.A. Brewer:** None.

Poster

598. Identifying Circuits in Striate Cortex

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 598.01/J45

Topic: D.04. Vision

Title: Organization of interareal connectivity in mouse cortex

Authors: ***J. A. HARRIS**[1], K. E. HIROKAWA[2], L. NG[2], S. MIHALAS[2], C. GERFEN[3], P. BOHN[2], B. OUELLETTE[2], M. MORTRUD[2], J. D. WHITESELL[2], S. SORENSEN[2], H. ZENG[2]; [1]Allen Inst. For Brain Sci., Seattle, WA; [2]Allen Inst. for Brain Sci., Seattle, WA; [3]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: The mouse cortex is densely interconnected in complex ways. Whether simpler underlying rules exist which govern these connections is currently not well understood. One possibility is that the mouse cortex is organized into a multi-level hierarchy, with anatomical features that differentiate between feedforward and feedback connections. To begin to explore whether this principle applies to mouse cortex, we used data from our Allen Mouse Brain Connectivity Atlas. Long-range axonal projections were mapped from genetically identified cell populations throughout the cortex using Cre driver lines and rAAV expressing Cre-dependent fluorescent protein (e.g. rAAV2/1.pCAG.FLEX.EGFP.WPRE.bGH). Fluorescently labeled axons were imaged by serial two-photon tomography at high throughput, high resolution, and with high sensitivity through the entire brain. Image series were registered into a common 3-D space, allowing for quantitation of signal, determination of spatial location, and relative topographical patterns between brains. Here, we present our analyses of cortical connectivity patterns from a set of 10 cortical areas and Cre driver lines used to selectively label types of projection neurons in layers 2/3 or 5. As a first step, we classified all projection patterns within each cortical target and assessed the frequency of occurrence of each type of pattern. Through this process, we identified ~10 distinct laminar patterns of termination in mouse cortex. The four most common types were; 1) equal density terminations across all layers, 2) preferential terminations in deep layers only, 3) preferential termination in superficial layers only, and 4) preferential termination in layer 1 and deep layers. Additional computational methods to classify termination patterns and analyze connectivity based on layer of origin as well as termination

patterns are used to determine whether there are general governing principles of mouse cortical organization that can be identified based on anatomical connectivity.

Disclosures: **J.A. Harris:** None. **K.E. Hirokawa:** None. **L. Ng:** None. **S. Mihalas:** None. **C. Gerfen:** None. **P. Bohn:** None. **B. Ouellette:** None. **M. Mortrud:** None. **J.D. Whitesell:** None. **S. Sorensen:** None. **H. Zeng:** None.

Poster

598. Identifying Circuits in Striate Cortex

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Topic: D.04. Vision

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Gatsby Charitable Foundation

Howard Hughes Medical Institute Gilliam Fellowship

University of California, San Diego Medical Scientist Training Program T32 GM007198-40

Title: Connectivity of Vasoactive Intestinal Peptide expressing inhibitory interneuron in mouse visual cortex

Authors: *E. M. KYUBWA[1,2], J. Z. HUANG[3], E. M. CALLAWAY[1];
[1]Salk Inst. for Biol. Studies, LA Jolla, CA; [2]Bioengineering, UCSD, La Jolla, CA; [3]Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Understanding how distinct cell types are wired to affect local circuits is important to understanding how cortical circuits function. Inhibitory GABaergic interneurons, although small in number, play a major role in increasing the computational power of cortical circuits. Distinct non-overlapping interneuron populations expressing markers such as Parvalbumin (PV), Somatostatin (SOM), and Vasoactive Intestinal Peptide (VIP) can be targeted using transgenic mouse lines. VIP cells are recruited during particular brain-states and behaviors and preferentially inhibit SOM cells in mouse neocortical layer 2/3. Earlier studies in rat cortex implicated Calretinin (CR) expressing interneurons in similar circuits, but overlap between CR

and SOM in mice led to an emphasis on VIP cells rather than CR. Only about 40% of VIP cells co-express CR (VIP+/CR+) leaving open the possibility that VIP+/CR+ cells might differ from VIP+/CR- neurons in their connectivity or function. To address this question, we take advantage of flp and Cre mouse lines, and an intersectional and subtractive adeno-associated virus (AAV) that expresses ChR2 under the control of flippase and Cre recombinase. We parsed out the VIP population into two groups, VIP+/CR+ and VIP+/CR-, to generate ChR2 expression in each subgroup. We performed *in vitro* slice whole-cell patch recordings simultaneously in SOM cells and pyramidal cells during full field optical stimulation of ChR2. We measured inhibitory postsynaptic currents (IPSC) and postsynaptic charge (IPSQ) and compared the ratios for the SOM/Pyramid pairs. As previously reported in VIP cells, during stimulation of VIP+/CR+ cells IPSCs were high in SOM cells and low in pyramidal cells. The IPSQ ratio in SOM cells and pyramidal cells was high in layer 2/3. During stimulation of VIP+/CR- cells, preliminary data suggest that the ratio of inhibitory input strength for SOM and pyramidal cells is the reverse of what is observed following stimulation of VIP+/CR+ cells; currents are larger in pyramids than in SOM neurons. These results suggest that VIP neurons are a heterogeneous population. We are also investigating other potential postsynaptic targets of VIP+/CR- interneurons to shed light onto the integration of these cells into cortical circuits and to provide further insight into their computational roles.

Disclosures: **E.M. Kyubwa:** None. **J.Z. Huang:** None. **E.M. Callaway:** None.

Poster

598. Identifying Circuits in Striate Cortex

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 598.03/J47

Topic: D.04. Vision

Title: Characterization and comparison of cortical and geniculate responses in awake and anesthetized mouse

Authors: *S. DURAND, R. IYER, K. MIZUSEKI, S. MIHALAS, C. REID;
Allen Inst. For Brain Sci., Seattle, WA

Abstract: The mouse has become one of the main models in the study of vision, but only in the past few years that the vision community has started studying awake mice to better understand the importance of behavior.So far, the most extensive survey studies describing characteristics of V1 and LGN responses have been done in anesthetized mice (Niell and Stryker, 2008 and Piscopo et al., 2013). Our recent work examines how V1 and LGN perform in awake mice.

Using simultaneous recordings with high density silicon probes from hundreds of cells in LGN and V1 of C57BL/6J mice, we analyzed visual response properties to diverse stimuli, including sparse noise and drifting gratings in awake mice, both stationary and running, as well as anesthetized mice. We found that some properties such as orientation tunings are consistent under different states, whereas other properties such as temporal frequency and contrast response curves appear altered. We further divided the cells recorded in putative inhibitory and excitatory cells, based on their spike shape (Niell and Stryker, 2008), and investigated each layer in V1. As seen in the anesthetized mice, putative inhibitory cells show distinct properties such as low orientation selectivity index, low F1F0 index and high receptive field size. Layer 5 putative excitatory cells also had these characteristics compared to other excitatory cells, although to a lesser extent than putative inhibitory cells in all layers. Our overall aim here is to provide a broad overview of visual response properties in V1 and LGN in awake mice that can be useful as a reference for the vision community.

Disclosures: **S. Durand:** None. **R. Iyer:** None. **K. Mizuseki:** None. **S. Mihalas:** None. **C. Reid:** None.

Poster

598. Identifying Circuits in Striate Cortex

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Topic: D.04. Vision

Support: NSF Graduate Research Fellowship

Mather's Foundation Grant

Allen Institute for Brain Science

Title: The influence of long-range feedback inputs on single-cell dendritic signaling

Authors: ***A. SHAI**[1,2], C. A. ANASTASSIOU[2], H. ZENG[2], M. E. LARKUM[3], C. KOCH[2]; [1]Bioengineering, Caltech, Pasadena, CA; [2]Allen Inst. for Brain Sci., Seattle, WA; [3]Humboldt Univ., Berlin, Germany

Abstract: Long-range feedback connectivity in the neocortex has been implicated in attention and consciousness [1,2]. What are the physiological effects mediating such top-down and perceptual influences, and what computational role do they play in the cortical network? In this work we study the role feedback axons have on single, layer 5 pyramidal neurons in mouse

primary visual cortex. In particular, we focus our attention on projections arising from anterior cingulate cortex and latero-medial area of the visual cortex. First, we use the method of sCRACM [3] to map the locations of synapses on the dendrites of single cells in V1 [4], and find that inputs arrive in two distinct groups on the dendrites - one in the basal dendrites in layer 5, and the other in the apical tufts, in layers 1 and 2. Then, using an in-vitro optogenetic preparation, we monitor the post-synaptic effects that light-evoked feedback axons have on whole-cell patched cells. We find that direct monosynaptic excitation from frontal regions that form synapses in the upper layers of the cortex manipulate the threshold for dendritic Ca-spikes, even when those synapses fail to elicit any appreciable response at the soma in isolation. Additionally, we characterize the similarities and differences of projections from multiple higher order areas onto single cells in primary visual cortex. We discuss a possible role for such feedback projections in the formation of perceptual representations [5], whereby feedback acts to regulate the frequency of firing in neurons that themselves make long-range projections to other areas of cortex and the thalamus. [1] Zhang, Siyu, et al. "Long-range and local circuits for top-down modulation of visual cortex processing." science 345.6197 (2014): 660-665. [2] Lamme, Victor AF, and Pieter R. Roelfsema. "The distinct modes of vision offered by feedforward and recurrent processing." Trends in neurosciences 23.11 (2000): 571-579. [3] Petreanu, L., T. Mao, et al. (2009). "The subcellular organization of neocortical excitatory connections." Nature 457(7233): 1142-1145. [4] Yang, Weiguo, et al. "Distinct balance of excitation and inhibition in an interareal feedforward and feedback circuit of mouse visual cortex." The Journal of Neuroscience 33.44 (2013): 17373-17384. [5] Larkum, Matthew. "A cellular mechanism for cortical associations: an organizing principle for the cerebral cortex." Trends in neurosciences 36.3 (2013): 141-151.

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Poster

598. Identifying Circuits in Striate Cortex

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Program#/Poster#: 598.05/K1

Topic: D.04. Vision

Support: NIH Grant R01EY023173

Title: Cellular taxonomy of the primary visual cortex in mice by single cell RNA-seq

Authors: *B. TASIC, V. MENON, T. N. NGUYEN, T. K. KIM, Z. YAO, K. SMITH, T. DOLBEARE, B. LEVI, T. JARSKY, S. SORENSEN, L. GRAY, D. BERTAGNOLLI, J. GOLDY, N. SHAPOVALOVA, S. PARRY, L. MADISEN, S. SUNKIN, S. MIHALAS, C. DANG, J. PHILLIPS, L. NG, A. BERNARD, C. KOCH, M. HAWRYLYCZ, H. ZENG; Allen Inst. For Brain Sci., Seattle, WA

Abstract: Nervous systems are composed of numerous cell types, but the extent of their diversity is poorly understood. We are pursuing the transcriptomic characterization of individual cells within the visual cortex of adult mice in two phases. For the first phase, we have employed full-length single cell RNA-seq to characterize more than 1600 cells isolated by FACS from a variety of transgenic Cre driver lines. We constructed cellular taxonomy using a purely data-driven "bottom-up" approach refined by machine learning algorithms. We have uncovered at least 49 cell types, of which 23 and 19 types correspond to inhibitory and excitatory neurons, respectively, and 7 types are non-neuronal. Additional analysis reveals that single cell transcriptomic phenotypes are distributed in the gene expression space in a combination of continuity and discreteness; we define cells that congregate well into uniform categories as 'core cells' and define cells that have transcriptional signatures of at least two cell types as 'transitional cells.' In addition, we discover new molecular markers for cell classification, analyze cell type-specific alternative splicing and characterize many transgenic Cre lines for cell type composition. This initial dataset has been used as a guide for other projects at the Allen Institute that are pursuing cellular characterization using other experimental approaches, and will be used for generation of new transgenic mice that will allow specific access to these cell types. To explore this data set, an online interactive scientific vignette application has been developed and can be viewed at: http://casestudies.brain-map.org/celltax. For the second phase of transcriptomic characterization of the primary visual cortex, we are evaluating a variety of different approaches for scaling up the sampling of inhibitory and excitatory neuronal classes in an unbiased manner. We plan to employ pan-excitatory and pan-inhibitory transgenic lines, and to collect an order of magnitude larger number of cells than in the previous phase from layer-specific dissections. This approach will also result in better information on location of specific cell types, as the dissection information will be mapped into the Allen Mouse Common Coordinate Framework. Finally, this information will be integrated with other data modalities (electrophysiological, morphological, etc.) to arrive at a refined cellular taxonomy of this well-defined cortical area.

Disclosures: **B. Tasic:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **V. Menon:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **T.N. Nguyen:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **T.K. Kim:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **Z. Yao:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **K. Smith:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **T. Dolbeare:** A. Employment/Salary (full or part-time):; Allen Institute for Brain Science. **B. Levi:** A.

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Poster

598. Identifying Circuits in Striate Cortex

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 598.06/K2

Topic: D.04. Vision

Support: ANR-09-SYSC-002-BALWM

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ANR-14-NEUC-0001-BASCO

France Israel Laboratory of Neuroscience

Title: The effect of the fine structure in connectivity on the collective dynamics in cortex

Authors: *C. A. VAN VREESWIJK[1], S. RAO[2], D. HANSEL[1];
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Abstract: There is increasing evidence for fine-structure in cortical connectivity [1]. Bidirectional connectivity and motifs of 3 or more highly interconnected neurons are more prevalent than expected from purely random connectivity [2]. What is the effect of these excess motifs on the collective dynamics in cortex? To address this question we investigate the dynamics of a network of neurons randomly connected with a rule such that the probability of directional connections is increased compared to the pure chance case (Poisson or Erdös-Renyi connectivity). The network consist of two populations of cells, excitatory (E) and inhibitory (I), and it operates in the 'standard' balanced regime [3]. Combining analytical calculations and extensive numerical simulations we show that excess bidirectional connections between the E cells or between I cells slow down the fluctuations in the neuronal activity. As a result, the autocorrelation of the neuronal activity decay more slowly than in the corresponding Poisson network. Comparing the contributions of E and I connectivity to this effect we show that, remarkably, bidirectional connections between I neurons are more efficacious in slowing down the dynamics. In contrast to bidirectional connections within the same population, bidirectional connections between populations decrease the correlation duration. The Fano factor of the spike count of neurons in sensory cortices decreases when stimuli are presented [4] and varies with the stimulus features [5]. Could the bidirectional connectivity explain these findings ? To investigate this we studied networks of conductance-based spiking neurons modeling V1 with and without an orientation map [6]. We found that bidirectional connectivity affects the Fano factor, both at rest and during stimulation and that the quantitative importance of this effect depends on the synaptic intrinsic dynamics. It is more pronounced when the synapses are slow than when they are fast. Finally, we show that these phenomena are due the small loops that the bidirectionality of the connections induces in the network architecture. Together with the relatively strong synapses these lead to an effective delayed self-coupling of neurons onto themselves, the effects of which are non-negligible because the network operates in the balance regime. [1] Y Yoshimura & EM Callaway Nat. Neurosci. (2005) [2] S Song, PJ Sjostrom, M Reigl, S Nelson, and DB Chklovskii. PLoS Biol. (2005). [3] C van Vreeswijk and H Sompolinsky, Science (1996) [4] MM Churchland et al. Nat. Neurosci. (2010) [5] SA Ponce-Alvarez et al. Proc. Nat. Acad. of Science (2013). [6] D Hansel & C van Vreeswijk, J. Neurosci (2012).

Disclosures: C.A. Van Vreeswijk: None. **S. Rao:** None. **D. Hansel:** None.

Poster

598. Identifying Circuits in Striate Cortex

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Program#/Poster#: 598.07/K3

Topic: D.04. Vision

Title: Automated creation of generalized leaky integrate-and-fire neuron models at several levels of complexity tuned to *in vitro* electrophysiology data

Authors: *C. M. TEETER, R. IYER, N. CAIN, D. FENG, S. SUNKIN, C. KOCH, S. MIHALAS;
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Abstract: For simulations of neural networks there is a tradeoff between the size of the network that can be simulated and the complexity of the model used for the individual neurons. A series of models of increasing complexity were constructed to reproduce the spiking behavior of the database of recorded neurons collected as part of the Allen Cell Types Database. Starting with a leaky integrate-and-fire model, three generalizations were added: a) after-spike currents which represent the slower effects of ion channels activated by an action potential, b) subthreshold voltage and spike-dependent changes in threshold caused by the activation and inactivation of ion channels, and c) voltage and threshold reset rules derived from the electrophysiology data. These rules determine how the threshold and voltage are reset after a spike and depend on the state prior to the action potential. Electrophysiological stimuli were specifically designed to estimate some of the parameters of the generalizations: short square pulse currents to determine the minimal instantaneous threshold, a series of such pulses to determine how the threshold is updated by spikes, and multiple instantiations of frozen noise at different amplitudes for the optimization and testing of the rest of the parameters. Following these initial estimates, some parameters were further tuned to optimize the reproduced spike times generated by a training noise stimulus. The optimization method was based on maximizing the likelihood of a model neuron with intrinsic noise exactly reproducing the spike train observed in the experiment. The model performance was subsequently evaluated on a test stimulus: for different time scales, the fraction of the variance of the neuronal response which was explained by the model was computed. In addition to characterizing the level of complexity that is needed to recreate spiking behavior, we are interested in characterizing sets of predefined cell classes by looking at the relation between model parameters and different cell types, as well as asking if such models can further refine or subdivide these classes.

Disclosures: **C.M. Teeter:** None. **R. Iyer:** None. **N. Cain:** None. **D. Feng:** None. **S. Sunkin:** None. **C. Koch:** None. **S. Mihalas:** None.

Poster

598. Identifying Circuits in Striate Cortex

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 598.08/K4

Topic: D.04. Vision

Title: Data generation pipeline for the allen cell types database

Authors: *C. KOCH, J. BERG, A. ARKHIPOV, S. SORENSEN, B. TASIC, C. ANASTASSIOU, S. SUNKIN, N. GOUWENS, S. MIHALAS, T. JARSKY, C. TEETER, T. DESTA, S. CALDEJON, S.-L. DING, N. GAUDREAULT, V. MENON, S. PARRY, K. SMITH, J. TING, W. WAKEMAN, E. LEIN, C. FARRELL, V. MALDONADO, H. PENG, C. DANG, M. HAWRYLYCZ, L. NG, A. BERNARD, H. ZENG, J. PHILLIPS;
Allen Inst. For Brain Sci., Seattle, WA

Abstract: The Allen Institute's Cell Types Program seeks to classify cell types in the adult mouse and human neocortex, beginning with a focus on mouse visual cortex and human lateral temporal cortex. The goal is to analyze single neurons based on electrophysiology, transcriptional signatures, dendritic morphology, projection targets and connectivity. Data from these different modalities will be used to derive a cell types taxonomy and to answer such basic questions as: Can every neocortical cell be assigned to a unique type? Is the number of such cell types much smaller than the number of cells? Do they tile the neocortical sheet? How do cell types differ across functionally distinct regions of the neocortex? Are cell types conserved between mice and humans, or do humans have unique cell types? For this purpose, we have established the Allen Cell Types Database. Here we overview the data generation pipeline for neurons from the lateral geniculate nucleus (LGN) and primary visual cortex (V1) of the young adult laboratory mouse. Slices prepared from P45 to P70 mice (an interneuron or cortical layer specific Cre driver line crossed to an Ai14 tdTomato reporter line) are imaged during the cutting process to aid in brain region identification and registration to the Allen Mouse Common Coordinate Framework (CCF). The CCF is a 3-D anatomical framework with 3-D structural annotations and 10 μm resolution. Neurons are then analyzed in various ways including: (i) electrophysiological characterization of their intrinsic firing properties based on somatic patch recordings using a standard stimulation paradigm; (ii) 3-D morphological reconstructions of the dendritic tree based on biocytin fills; (iii) a variety of quantitative abstract point models (generalized, leaky integrate-and-fire or GLIF models) as well as biophysically grounded spatially extended compartmental models that are fitted to the electrical and morphological data for individual neurons; and (iv) the RNA species expressed by these cells using single cell transcriptomics. The data and relevant metadata are publicly available via the Allen Brain Atlas data portal (www.brain-map.org), together with search and visualization tools, and are fully integrated with other Allen Brain Atlas resources.

Disclosures: C. Koch: None. **J. Berg:** None. **A. Arkhipov:** None. **S. Sorensen:** None. **B. Tasic:** None. **C. Anastassiou:** None. **S. Sunkin:** None. **N. Gouwens:** None. **S. Mihalas:** None. **T. Jarsky:** None. **C. Teeter:** None. **T. Desta:** None. **S. Caldejon:** None. **S. Ding:**

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Poster

598. Identifying Circuits in Striate Cortex

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 598.09/K5

Topic: D.04. Vision

Title: Genetic labeling strategies for *in vitro* functional analysis of human neocortical cell types and microcircuits

Authors: P. CHONG[1], *J. T. TING[1], T. L. DAIGLE[1], R. P. GWINN[2], C. COBBS[3], E. LEIN[1]; [1]Allen Inst. For Brain Sci., Seattle, WA; [2]Epilepsy Surgery and Functional Neurosurg., [3]The Ben and Catherine Ivy Ctr. for Advanced Brain Tumor Treatment, Swedish Neurosci. Inst., Seattle, WA

Abstract: Understanding the structure and function of the human brain in health and disease represents one of the great scientific challenges of the 21st century. Modern technological advances in molecular neuroscience have enabled extensive breakthroughs in exploring brain function with refined spatial and temporal precision in genetically tractable animal model systems (e.g. mice, rats, fly, worm). Specifically, molecular genetic approaches have enabled precise targeting, lesion, monitoring, and manipulation of cell types and neural circuits in the context of whole animal behaviors, although these techniques have been generally unavailable to study non-genetically manipulable organisms including humans. However, several laboratories have demonstrated the feasibility of performing detailed mechanistic and functional investigations *in vitro* using living tissues from neurosurgical resections, opening the possibility for *in vitro* application of molecular genetic tools to study local brain circuits in human. To advance this approach, we have developed capabilities for electrophysiological, morphological, and transcriptomic analysis of individual human neocortical cells in acute brain slices derived from neurosurgeries. We have also developed capabilities for extended analysis on human brain slice maintained in an incubator for 1-10 days, thereby allowing implementation and exploration of genetic labeling of neocortical cell types using diverse viral transgene expression strategies. Using these preparations, we demonstrate successful human brain slice transduction using Herpes Simplex Virus (HSV), Adeno-associated virus (AAV), and Adenovirus, and conducted a

time course analysis of transgene expression. Furthermore, we have begun to evaluate novel viral vectors for fluorescent labeling of subsets of human neurons for targeted patch clamp recordings as well as viral vectors for optogenetic stimulation to facilitate interrogation of synaptic connectivity in neocortical microcircuits. Collectively, these approaches aim to provide selective molecular genetic targeting and manipulation to identify and study specific features of human neocortical cell types and local circuits.

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Poster

598. Identifying Circuits in Striate Cortex

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Program#/Poster#: 598.10/K6

Topic: D.04. Vision

Title: Standardizing spike sorting: an *in vitro*, in silico and *in vivo* study to develop quantitative metrics for sorting extracellularly recorded spiking activity

Authors: *C. MITELUT[1,2], S. L. GRATIY[2], D. DENMAN[2], J. H. SIEGLE[2], S. DURAND[2], K. GODFREY[2,1], C. LEE[2], R. C. REID[2], M. HAWRYLYCZ[2], C. KOCH[2], N. V. SWINDALE[1], C. ANASTASSIOU[2];
[1]Univ. of British Columbia, Vancouver, BC, Canada; [2]Allen Inst. for Brain Sci., Seattle, WA

Abstract: Detecting neural dynamics at the single-cell level is central to many experimental investigations of the brain. The most common way of monitoring such dynamics *in vivo* is by recording brain activity from individual electrodes or high-density silicon probes inserted in the brain of the living animal. Extracting, separating and ascribing “spikes” to individual neurons from such recordings, i.e. spike sorting, is challenging given the similar shape of spikes from purportedly different cells [Swindale and Spacek, 2014]; spike sorting becomes significantly more CPU-demanding with increasing numbers of recording sites [Rossant et al 2015]. Additionally, while a number of algorithms and sorting suites have been developed over the past two decades, there are very few realistic ground-truth data-sets to test them against. We developed unique and previously unavailable *in vitro*, in silico and *in vivo* ground truth data-sets to generate quantitative sorting metrics and characterize sorting performance for separate spike sorting stages: spike detection, clustering and manual cleanup. Specifically, we used concurrent intracellular and extracellular recordings from various cell types in rodent slices to obtain realistic single-neuron extracellular spike signatures [Anastassiou et al, in press]. In silico, we

used biophysically and morphologically realistic single-cell representations [Hay et al 2011, 2013; Hu et al 2010; Norenberg et al 2010] to create a cortical patch consisting of ~5,000 synaptically connected spiking cells responding to various external inputs while emulating extracellular depth recordings along the patch. Finally, high-density extracellular recordings were acquired *in vivo* from rodent visual cortex for standardized visual inputs. Using these datasets we determine Receiver Operator Characteristic (ROC) curves for several spike detection thresholds and methods. Following blind spike sorting tests of our data-sets we benchmark speed, resource demands and overall quality of output for several sorting algorithms including: Klustakwik [Rossant et al 2015], SpikeSorter [Swindale and Spacek 2014], Osort [Rutishauser et al 2006]. We develop two sorting metrics, i.e. completeness and purity, and show that the quality of a sorted unit depends not only on its peak-to-peak (PTP) amplitude but also on the sorting algorithms employed. Lastly, we show that several sorting parameters can be determined automatically thus reducing supervision-demand of sorting tasks while preserving the overall quality of output.

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Poster

598. Identifying Circuits in Striate Cortex

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 598.11/K7

Topic: D.04. Vision

Title: Characterizing the mesoscale organization of mouse visual cortex using ultraviolet light

Authors: *J. SIEGLE[1], J. ZHUANG[1], D. J. DENMAN[1], M. T. VALLEY[1], B. P. DANSKIN[1], R. C. REID[1], S. R. OLSEN[1], J. WATERS[1], T. J. BLANCHE[1,2];
[1]Allen Inst. for Brain Sci., Seattle, WA; [2]UC Berkeley, Berkeley, CA

Abstract: The mouse retina contains cones that are sensitive to ultraviolet (UV) wavelengths, and mice show behavioral responses to UV light. However, the manner in which UV stimuli are processed at the level of visual cortex has yet to be investigated. We placed mice in an immersive dome environment capable of presenting full-field human-visible (400-700 nm) and UV (350-380 nm) stimuli. In N = 8 Emx1-Cre x Ai96 (GCaMP6s reporter) mice, which express calcium-sensitive fluorescent proteins in cortical excitatory neurons, we mapped the retinotopic organization of visual cortex using through-skull widefield imaging of the dorsal cortical surface.

Checkerboard patterns swept across the visual field in azimuth and elevation led to robust increases in fluorescence (mean maximum ΔF/F across mice = 11.1 ± 4.3%), which were converted into visual sign maps to delineate the borders of V1 and higher visual areas. For both human-visible and UV stimulation, we compared the number of identifiable areas, areal boundaries and retinotopic coverage, and the relative activation strength of each region.

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Poster

598. Identifying Circuits in Striate Cortex

Location: Hall A

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Program#/Poster#: 598.12/K8

Topic: D.04. Vision

Title: Active somatic and dendritic single-cell models using data from an *in vitro* slice electrophysiology and morphology platform

Authors: ***C. ANASTASSIOU**[1], W. VAN GEIT[2], C. ROSSERT[2], J. BERG[1], T. DESTA[1], D. FENG[1], L. KANARI[2], S. SUNKIN[1], J. SHILLCOCK[2], S. SORENSEN[1], H. PENG[1], A. BERNARD[1], C. DANG[1], M. HAWRYLYCZ[1], S. HILL[2], J. W. PHILLIPS[1], H. ZENG[1], E. MUELLER[2], H. MARKRAM[2], C. KOCH[1];
[1]Allen Inst. for Brain Sci., Seattle, WA; [2]Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland

Abstract: The Allen Institute has recently established the Allen Cell Types Database, with the goal of collecting electrophysiological, morphological, and transcriptional data from individual neurons of the mouse and human brain (e.g., see poster-abstracts by Berg et al and Sorensen et al). As part of this effort, the aim is also to construct and test biophysically and morphologically detailed conductance-based models, emulating the neural response to stereotyped somatic electrophysiological stimuli. Towards this end, in a joint effort between the Allen Institute and EPFL's Blue Brain Project (BBP), experimental (slice electrophysiology and morphology) single-neuron data are used to analyze and construct morphologically detailed compartmental models that faithfully reproduce many aspects of the physiology of these neurons using technology developed by the BBP. Crucially, these single-neuron representations include active dendritic conductances to capture key features of synaptic integration as observed in the mammalian brain. For such active representations to be developed, we use a computational framework based on genetic optimization [Druckmann et al, 2007; Hay et al, 2011]. Specifically,

we instantiate and examine three options for the optimization setup: (1) a soma-centric approach with spatial distribution of active conductances aiming to capture only somatic subthreshold and spiking features (2) a soma- and dendrite-centric approach including dendritic features (such as BAP-speed, BAP-width, input resistance, Vrest as function of apical distance) as measured experimentally (e.g. [Shai et al, *PLoS Computat Biol*, 2015] (3) a soma- and dendrite-centric approach including a Ca-hotzone at the main apical bifurcation and accounting for critical frequency experiments as measured in the literature (e.g. [Shai et al, *PLoS Computat Biol*, 2015]). Each optimization runs in parallel on up to 8192 cores on a Blue Gene Q supercomputer. The accuracy of the resulting models is assessed via a spectrum of metrics (e.g. explained variance, etc.) Crucially, these detailed single-neuron models, along with the electrophysiology and morphology data from the same single-neuron will part of the Allen Institute Cell Types Database and the Human Brain Project Neuroinformatics Platform.

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Poster

598. Identifying Circuits in Striate Cortex

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Topic: D.04. Vision

Title: Chromatic responses in the mouse central visual pathway

Authors: *D. J. DENMAN[1], J. H. SIEGLE[1], R. C. REID[1], T. J. BLANCHE[1,2];
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Abstract: The mouse retina contains two cone photopigments: a medium-wavelength opsin (M) with a peak sensitivity at ~520 nm, in the green region of the spectrum, and a short-wavelength opsin (S) with a peak sensitivity at ~360nm, in the UV-A region. These opsins are expressed and co-expressed non-uniformly across the retina, with M-opsin responses dominating dorsal regions and S-opsin responses dominating ventral regions. These chromatic sensitivities are also apparent in bipolar and retinal ganglion cell responses. In spite of this, the mouse dorsal lateral geniculate nucleus (dLGN) and primary visual cortex (V1) have primarily been studied under

photopic conditions using monochromatic stimuli well-suited for the M-opsin, but providing little to no photoexcitation of the S-opsin. We characterized single-cell and population dLGN and V1 responses using high-density silicon array recordings to both monochromatic UV-A and green stimuli. Full-field visual stimuli were presented using an immersive visual stimulation environment and a custom-modified DLP projector capable of generating monochromatic stimuli centered on 360nm or 525nm, under mesopic luminance conditions (2cd/m2 for 525nm, ~3x efficacy for 360nm). Chromatic response clustered into three categories: UV-dominated, green-dominated, and nearly equal UV~green (achromatic). Most recording sites contained a mix of these classes. Chromatic balance was visuotopically organized, with UV-dominant responses more prevalent in the upper visual field and green-dominant more prevalent in the lower visual field. Preliminary results indicate an imbalance toward green in OFF responses, while ON responses were more chromatically balanced. Our results support the existence of chromatic processing without evidence for chromatic opponency in the mouse visual system.

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Poster

598. Identifying Circuits in Striate Cortex

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ANR-14-NEUC-0001-BASCO

France Israel Laboratory of Neuroscience

Title: The mechanism of orientation selectivity in Layer 4 in rodent V1

Authors: *D. HANSEL[1,2], G. MATO[3], C. VAN VREESWIJK[1,2];
[1]CNRS, Paris, France; [2]Ctr. for Neurophysics, Physiol. and Pathology, Univ. Paris Descartes, Paris, France; [3]Ctr. Atomico, Bariloche, Argentina

Abstract: Neurons in primary visual cortex (V1) exhibit orientation selectivity (OS). This is true for animals like cats or primates in which V1 has an orientation map (OM) as well as for those without OM (salt-and-pepper organization), e.g. rodents. Whether OS is primarily due to feedforward (FF) connectivity or to recurrent interactions has not been settled. In the former case the presence or absence of an OM hardly matters, but in the latter the spatial organization of preferred orientations (PO) could affect the mechanism. The connectivity in rodent V1 is hotly debated. Unclear is the extent to which connections in adult mice are specific. With specificity, the distribution of the POs of cells projecting to a neuron would be similar to that in cat V1 and the same mechanism could operate in both cases. In contrast, with random connectivity this distribution is flat. Importantly, it has been demonstrated that in mice V1 neural responses are highly selective at eye opening although the connections are not yet specific (Ko etal, 2013). How can OS arise in this case? In a recent theoretical paper (Hansel & van Vreeswijk, 2012) we showed that strong OS emerges naturally in layer 2/3 in V1 if it operates in the balanced excitation/inhibition regime even if the recurrent connectivity is random and FF inputs from Layer 4 (L4) result from selective neurons with random preferred orientations. A question then arises : But how do L4 neurons exhibit OS in rodents ? To address this issue we consider a model comprising two networks, one for L4 and one for the LGN. We assume first circular LGN receptive fields and purely random FF connections. We show that despite the lack of OS in LGN the FF connectivity carries a weak information on the stimulus orientation which can be extracted and amplified by the L4 network if it operates in the balanced regime. We show that the orientation selectivity index (OSI) depends only weakly on the model parameter with typical mean OSI=0.1-0.2 and 0.15-0.3 for the F0 and F1 components of the response. We also find that for realistic parameter values, the F0 component is substantially less tuned for inhibitory neurons than for excitatory neurons but for F1 components tuning is similar in both populations. Additional contributions to the OS in L4 with salt and paper organization can come from LGN neurons if they have elongated center-surround receptive fields, as recently described in experimental studies or in specificity in the LGN projections as in the Hubel & Wiesel mechanism. We show that these three contributions can be unambiguously disentangled experimentally by characterizing how the PO of the neurons varies with the spatial frequency of a drifting grating stimulus.

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Poster

598. Identifying Circuits in Striate Cortex

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 598.15/K11

Topic: D.04. Vision

Title: Generation and analysis of biophysical models of diverse mouse cortical neuron types

Authors: *N. W. GOUWENS, J. BERG, T. DESTA, D. FENG, T. FLISS, K. GODFREY, T. JARSKY, L. NG, S. SORENSEN, S. SUNKIN, Z. ZHOU, A. BERNARD, C. DANG, H. PENG, J. PHILLIPS, H. ZENG, M. HAWRYLYCZ, C. KOCH, A. ARKHIPOV;
Allen Inst. For Brain Sci., Seattle, WA

Abstract: The experimental data collected as part of the recently established Allen Cell Types Database contributes to an integrated framework for understanding the components of mouse cortical circuits. In close coordination with these experimental efforts, we have generated biophysically detailed models of individual neurons in that database, providing components for computational studies of neuronal cell types in the context of circuit function. The purpose of these biophysically detailed models, built from matching electrophysiological and morphological data collected from individual neurons recorded in slices, is to characterize the firing properties of different cell types and relate them to generalized biophysical mechanisms governing this firing. We construct the models by importing the reconstructed 3D morphologies of cells into the NEURON simulation environment and placing at the soma a set of 10 active conductances, as well as a mechanism describing intracellular Ca^{2+} dynamics. A leak conductance is also included in all compartments. For each model, the densities of these conductances and parameters of the $[Ca^{2+}]_i$ dynamics are optimized with a genetic algorithm to match a set of 12 electrophysiological features measured from the original cell's responses to step current injection. In most cases, we obtain relatively close matches to the original experimental data, as assessed by features of action potential shape (e.g., peak, depth, and width) and firing pattern (e.g., average firing rate, degree of adaptation) being within one or two experimentally-measured standard deviations or otherwise pre-defined tolerances of a particular feature. We further test the models produced by this procedure by applying all the other stimuli used in the original recordings and comparing the model responses to the recordings. Applying this technique to a diverse set of neurons from the mouse cortex, we analyze how well the resulting models generalize to various stimuli under different circumstances and compare characteristics of the models across subsets of cells (defined by Cre-based labels and location in the cortex). The optimized models are openly accessible online alongside the original experimental data as part of the public Allen Cell Types Database, and source code to run the models can be downloaded from the Allen Software Development Kit.

Disclosures: **N.W. Gouwens:** None. **J. Berg:** None. **T. Desta:** None. **D. Feng:** None. **T. Fliss:** None. **K. Godfrey:** None. **T. Jarsky:** None. **L. Ng:** None. **S. Sorensen:** None. **S. Sunkin:** None. **Z. Zhou:** None. **A. Bernard:** None. **C. Dang:** None. **H. Peng:** None. **J. Phillips:** None. **H. Zeng:** None. **M. Hawrylycz:** None. **C. Koch:** None. **A. Arkhipov:** None.

Poster

598. Identifying Circuits in Striate Cortex

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 598.16/K12

Topic: D.04. Vision

Title: Characterization of connectivity and synaptic properties of layer 4 neurons in the mouse primary visual cortex

Authors: G. J. SOLER-LLAVINA, *B. R. LEE, H. ZENG;
Allen Inst. for Brain Sci., Seattle, WA

Abstract: The connectivity patterns and the synaptic properties among distinct cell types are essential to information flow and processing in the brain. There is a wealth of information regarding cell types and connectivity in many brain regions. However, at the level of resolution relevant to neuronal computation, our understanding of the numbers and kinds of cell types in a given neuronal circuit, their detailed connectivity and the properties of these connections remains incomplete. A goal of the Allen Institute for Brain Science is to create a more comprehensive classification of neuronal types with an initial focus on the mouse primary visual cortex (V1). We seek to create a full connectivity and synaptic properties profile of potential excitatory neurons in layer 4 (L4) of V1 using Cre-driver mouse lines that label sub-populations of cells, in combination with multi-whole cell recordings and optogenetics. In addition to implementing standardized and generalizable paradigms to comprehensively characterize synaptic properties, we aim to gain insight into the following questions: 1) Are patterns of connectivity a property of cell types? 2) Do unitary post-synaptic responses and short-term synaptic plasticity and postsynaptic receptor composition enable further differentiation of cell types? These questions are particularly interesting in the context of L4, which based on classical classification methods, appears to be formed by a homogeneous neuronal population. Our results suggest that there are at least two distinct populations of excitatory neurons coexist in L4 of the mouse V1.

Disclosures: G.J. Soler-Llavina: None. **B.R. Lee:** None. **H. Zeng:** None.

Poster

598. Identifying Circuits in Striate Cortex

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 598.17/K13

Topic: D.04. Vision

Title: A fine ultra-structural analysis of synaptic terminals formed by different cell types in layer 4 of the primary visual cortex of the mouse

Authors: *A. L. BODOR[1], K. GLATTFELDER[2], S. MIHALAS[2], M. TAKENO[2], N. M. D. COSTA[2];
[1]Allen Inst. For Brain Sci., Seattle, WA; [2]Allen Inst. for Brain Sci., Seattle, WA

Abstract: Layer 4 of the primary visual cortex (V1) provides one of the classical examples of cortical computation. It receives excitatory synapses from multiple sources including the thalamus, other cortical layers and its own recurrent connections. The detailed connectivity between these different partners and dendrites in layer 4 of mouse V1 is however largely unknown. Using serial section electron microscopy we provide a quantitative and detailed morphological analysis of the synapses formed by three different cell types whose axonal arbours innervate layer 4: thalamic, layer 6 corticothalamic neurons and local layer 4 neurons. Different cell types were labeled by immunohistochemistry against VGluT2 (thalamic boutons) or tdTomato expressed in layer 4 (Nr5a line) or layer 6 (Ntsr1 line) neurons. After regions of layer 4 were prepared for electron microscopy, labeled boutons were selected based on random sampling and the physical disector and then reconstructed from serial sections. Thalamic boutons were mostly polysynaptic, targeted mostly spines, and formed the largest synapses, though the distribution of synapse sizes was very broad. Layer 6 cells were highly variable in the number of synapses per bouton, their synapses were the smallest, and while they preferentially targeted spines, approximately 30% of their targets were dendritic shafts. Layer 4 recurrent connections formed mostly one synapse per bouton, the synapses were of a medium size, and like the thalamic boutons, they mostly targeted spines. Our results show that synapses formed by different cell types in layer 4 of mouse V1 display different morphological features. Similar to other animal models of layer 4, thalamic synapses were the largest and layer 6 synapses the smallest, but a notable difference is that rodent synaptic terminals are more polysynaptic. The described differences can also, in principle, be used to classify different cell types based on fine ultra-structural properties.

Disclosures: **A.L. Bodor:** None. **K. Glattfelder:** None. **S. Mihalas:** None. **M. Takeno:** None. **N.M.D. Costa:** None.

Poster

598. Identifying Circuits in Striate Cortex

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 598.18/K14

Topic: D.04. Vision

Support: HFSP LT-000173/2013

Title: The functional organization of presynaptic neural networks providing input to individual cortical neurons

Authors: *S. TRENHOLM[1], A. WERTZ[1], K. YONEHARA[1], Z. RAICS[1], M. LEINWEBER[1], D. HILLIER[1], G. SZALAY[2], G. KELLER[1], B. ROZSA[2], K.-K. CONZELMANN[3], B. ROSKA[1,4];
[1]Friedrich Miescher Inst., Basel, Switzerland; [2]Inst. of Exptl. Med., Budapest, Hungary; [3]Ludwig-Maximilians-Universitat, Munich, Germany; [4]Univ. of Basel, Basel, Switzerland

Abstract: Introduction: Many cortical neurons respond selectively to specific cues. For instance, in visual cortex, many neurons preferentially respond to specific orientations or directions of moving images. How this selectivity relates to that of the presynaptic network which spans across cortical layers remains unclear. Methods: Using single-cell-initiated, monosynaptically-restricted, retrograde transsynaptic tracing with rabies viruses expressing GCaMP6s, we imaged, *in vivo*, visual motion evoked activity of individual layer 2/3 pyramidal neurons and their presynaptic neuronal networks across cortical layers in primary visual cortex in mouse. Results: This technique labelled ~400 presynaptic cells connected to individual layer 2/3 pyramidal cells in primary visual cortex. The majority of presynaptic neurons were nearby in primary visual cortex, and cells were labelled across all cortical layers. Longer range connections were also consistently found, including inputs from the thalamus. Next, using *in vivo* calcium imaging we characterized the response properties to moving visual stimuli of the electroporated cell (i.e. the postsynaptic cell) as well as the response properties of the local presynaptic network in primary visual cortex. We found that presynaptic networks connected to individual layer 2/3 pyramidal cells could be classified into different groups based on functional organization. Conclusion: These results reveal the existence of different presynaptic network organization principles belonging to layer 2/3 pyramidal neurons.

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Poster

598. Identifying Circuits in Striate Cortex

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Support: DOE SciDAC Program

NNSA PSAAP

NIH RO1 EY019743

NSF IOS-1355075

Research to Prevent Blindness

Title: Large scale imaging and 3d visualization of long-range circuits in clarity-treated primate visual cortex

Authors: C. CHRISTENSEN[1], F. FEDERER[2], A. GOOCH[1], S. MERLIN[2], V. PASCUCCI[1,3], *A. ANGELUCCI[2];
[1]Scientific Computing and Imaging Inst., Univ. of Utah, Salt Lake City, UT; [2]Ophthalmol Moran Eye Ctr., Univ. Utah, Salt Lake Cty, UT; [3]Pacific Northwest Natl. Lab., Richland, WA

Abstract: Understanding the circuitry of the brain is necessary to understanding brain function. Recently there has been a renaissance in neuroanatomy, thanks to the discovery of cell-type specific tracers, and new methods for high-resolution imaging and 3D reconstruction of large data sets at much greater speed than previously possible. However, the large size and complexity of the primate brain, compared to mouse brain, poses greater challenges to the study of neural circuits. CLARITY tissue clearing (Chung et al. 2013) allows imaging labeled circuits through entire tissue blocks, without the need for tissue sectioning and section-to-section alignment. However, the large primate brain requires long image acquisition times, and software capable of compiling and stitching very large data sets, and tracing through these volumes. Here we have labeled projection neurons between visual cortical areas V1 and V2 in primates, using GFP-expressing AAV9. Tissue blocks were cleared using passive CLARITY technique (PACT; Yang et al. 2014), and imaged in a 2-photon microscope. A 1mm diameter injection site in V2 labeled a field of axons in V1 of about 60mm^3. Imaging a 5mm^3 volume at 1 μm z-resolution took 96 hrs, generating 130 GB of data. Hence, imaging the 60mm^3 V1 block would take 19 days, and produce 1.6 TB of data. To address the challenges posed by handling large data sets we adopted the ViSUS streaming platform for scalable data analysis and visualization (Pascucci et al. 2012). This is designed around an innovative notion of hierarchical space-filling curves that enables selective data access both locally and remotely. Its combination with progressive algorithms enables a dynamic scripting layer that provides on-the-fly computation of derived quantities such as statistics on the data or multiple concurrent maximum intensity projections from arbitrary directions. Remote data access is enabled with a server. Locating the server at the acquisition source allows data conversion so that the 3D images can be viewed during acquisition. View-

dependent, progressive resolution data streaming allows clients fast access to regions of interest while client-side caching amortizes network transfer costs, effectively hiding them from the user. The ease of data access provided by the ViSUS framework facilitates the alignment of 3D volumes while providing interactive access to the full data collection, so that a user can more easily switch among the tasks of data alignment, analysis and annotation. The end result is the presentation of data collections as single, large volumes that can be handled easily and interactively by multiple users in collaboration over a distributed environment.

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Poster

598. Identifying Circuits in Striate Cortex

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 598.20/K16

Topic: D.04. Vision

Title: Morphological classification of genetically-identified neurons in mouse primary visual cortex

Authors: *S. A. SORENSEN, T. DESTA, M. FISHER, A. HENRY, D. SANDMAN, N. THATRA, X. LIU, Z. ZHOU, J. BERG, S. CALDEJON, N. GAUDREAULT, T. LEMON, S. PARRY, J. HARRINGTON, W. WAKEMAN, D. FENG, S. SUNKIN, A. BERNARD, L. NG, C. DANG, H. PENG, J. PHILLIPS, C. KOCH, H. ZENG;
Neurosci., Allen Inst., Seattle, WA

Abstract: The Allen Institute for Brain Science has undertaken a large-scale effort to understand the full diversity of cell types in the mouse brain. We have focused our initial efforts on primary visual cortex (V1) in a range of layer- and interneuron-specific Cre driver mice crossed to TdTomato (tdT) reporter mice. Through a multi-modal characterization of single neurons, including electrophysiological, morphological and transcriptional studies, we aim to identify the crucial features that define a cell type, and to use them to establish a taxonomy of cell types for this brain region. These data will be made publicly available as part of the Allen Institute Cell Types Database. Electrophysiological experiments begin with a whole cell recording targeted to tdT-positive neurons in acute slices maintained *in vitro*. Intrinsic properties are recorded and cells are simultaneously filled with biocytin. For morphological studies, slices are then fixed, and stained for biocytin with an ABC-DAB reaction. Whole mount slices are then imaged with a widefield microscope at 20x (whole slice overview) and 63x (multi-plane image of biocytin-

filled neuron) to allow for regional identification and 3-dimensional reconstruction of individual neurons. Using Vaa3D software (http://www.vaa3d.org), semi-automated reconstructions of the dendrites, soma and the initial part of the axon are obtained for all neurons (>100) that have high data quality and/or value scores. A smaller subset of neurons has a reconstruction of the full axon that appears in the slice. Image and reconstruction data are then used to qualitatively map each reconstructed neuron to a putative morphological cell type and/or a set of correlated features. This analysis reveals the range of morphological types_as it relates to our existing knowledge_represented in this initial dataset. This information also provides a benchmark for data driven approaches to defining morphological cell types (presented in a separate poster by Xiaoxiao Liu et al.). This is a first step toward classifying neurons based on objective measures of their morphology. Morphologically-defined cell types will later be integrated with electrophysiologically- and transcriptionally-defined cell types, in order to generate a comprehensive description of neuronal cell types in mouse V1.

Disclosures: **S.A. Sorensen:** None. **T. Desta:** None. **M. Fisher:** None. **A. Henry:** None. **D. Sandman:** None. **N. Thatra:** None. **X. Liu:** None. **Z. Zhou:** None. **J. Berg:** None. **S. Caldejon:** None. **N. Gaudreault:** None. **T. Lemon:** None. **S. Parry:** None. **J. Harrington:** None. **W. Wakeman:** None. **D. Feng:** None. **S. Sunkin:** None. **A. Bernard:** None. **L. Ng:** None. **C. Dang:** None. **H. Peng:** None. **J. Phillips:** None. **C. Koch:** None. **H. Zeng:** None.

Poster

598. Identifying Circuits in Striate Cortex

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Program#/Poster#: 598.21/K17

Topic: D.04. Vision

Support: 5R01NS074015-06

Title: Simulating LFP responses in mouse V1 to sensory inputs using a large-scale, biophysically detailed multi-layer circuit model

Authors: ***S. L. GRATIY**[1], C. MITELUT[2], S. DURAND[1], D. DENMAN[1], J. SIEGLE[1], J. BERG[1], S. SORENSEN[1], A. ARKHIPOV[1], M. HINES[3], A. SHAI[4], J. PHILLIPS[1], H. ZENG[1], R. REID[1], M. HAWRYLYCZ[1], C. KOCH[1], C. ANASTASSIOU[1];
[1]Allen Inst. for Brain Sci., Seattle, WA; [2]Univ. of British Columbia, Vancouver, BC, Canada; [3]Yale Univ., New Haven, CT; [4]Caltech, Pasadena, CA

Abstract: Despite enormous progress in characterizing the properties of individual neurons and their connections, the mechanisms underlying processing of sensory stimuli in cortex remains largely unknown. Biophysically detailed models of neuronal circuits are well positioned to address this challenge since they naturally allow for the integration of anatomy, connectivity and physiology while predicting signals across multiple modalities: spikes, extracellular potentials and calcium imaging. With the aim of unraveling the biophysics of computation in mouse V1, we use modeling to explain the laminar LFP response to full-field flash visual stimuli during early stages of cortical processing (<50 ms). We developed a large-scale, biophysically detailed model of a multi-layer circuit in mouse V1 (corresponding to ~0.5 mm2 of cortical surface) utilizing reconstructed single cell morphologies and biophysical properties as well as cell type-specific connectivity rules. Each layer consists of one excitatory and one inhibitory cell-type represented by several different biophysically detailed templates. The model is capable of predicting multi-electrode array recordings such as unit activity and local field potentials [Buzsaki et al, Nat Rev Neurosci, 2012]. Using full-field flash LGN recordings as input to the model we reproduce in silico the stereotypical laminar pattern of LFP recordings [Niell & Stryker, J. Neurosci, 2008] as well as firing activity during resting and stimulus. We aim to 1) compute the laminar LFP profiles of activity of individual neuronal population and then 2) tune connectivity between the populations of different cell-types to match simulations to data. Thereby, we expect to infer the pathways of information processing in mouse V1 at the mesoscopic scale corresponding to that of LFP recordings.

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Poster

598. Identifying Circuits in Striate Cortex

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Support: NIH grant R01 EY019743

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Research to Prevent Blindness

Title: V1 layer 4B neurons projecting to V2 thick stripes in macaque: V1 intra-laminar projections and their relationship to cytochrome oxidase compartments

Authors: *J. T. YARCH, F. FEDERER, A. ANGELUCCI;
Moran Eye Inst., Univ. of Utah, Salt Lake City, UT

Abstract: Neurons in layer 4B of macaque primary visual cortex (V1) send their outputs to functionally different cortical areas and areal compartments. The unique contributions of 4B inputs to different cortical targets may result from differences in their anatomical wiring. Based on dendritic morphology, two 4B cell types have been recognized (spiny stellates, pyramids). Area MT receives 80% of 4B inputs from stellates, while V2 receives 80% of inputs from 4B pyramids (Nassi & Callaway 2007). However, V2 consists of distinct cytochrome oxidase (CO) stripe compartments, and we showed that thick stripes receive ~50% of 4B inputs from stellates (Yarch et al 2013). It is unclear whether 4B cells projecting to different targets also show unique intra-V1 axonal arbor patterns, or even whether such patterns can be used to classify cells. Previous reconstructions of 4B cells randomly filled intracellularly in V1 slices have shown stereotypical axon projection patterns: all 4B cells branch in layers 2/3, 4B and 5, with projections to 2/3 residing in CO blobs irrespective of soma location (Callaway & Wiser 1996). However, the areal targets of these 4B neurons were unknown in these studies. We have characterized the intra-V1 axonal branching patterns of 4B cells projecting to V2 thick stripes to uncover the anatomical foundations for the parallel streams between V1 and V2 (Federer et al. 2009,2013). Small injections of G-deleted-GFP rabies virus were targeted to V2 thick stripes identified by intrinsic optical imaging (3 macaques). GFP filled neurons in V1 L4B (n=19) were fully reconstructed through serial sections. Measurements of total axonal length contributed by each cell in each V1 layer allowed us to classify cells into 2 classes: 1) Class 1 cells (~61% of total) which branch in supragranular (SG, 4B only or 4B and 2/3) and infragranular (IG, mainly 5) layers (as described by Callaway and Wiser, 1996), 2) Class 2 cells (~39%) that only branch in IG layers (not previously described). On average, Class 1 and 2 cells dedicate 63% and 0%, respectively, of their axonal arbor to SG layers. Class 1 and 2 cells are 61% and 71%, respectively, spiny stellates, and both classes have somas that reside in interblobs or at blob borders; 1 soma in our reconstructed sample resided in a blob. For each cell we analyzed bouton positions relative to blobs in all layers. Irrespective of cell class, IG and SG axon branches avoid CO blob columns; instead, they target predominantly interblobs if their soma lies under an interblob, or blob borders if their soma lies under a border. Axon branches of the cell with its soma in a blob avoided blobs. Overall, lateral projections of 4B cells of either class show CO compartment specificity.

Disclosures: J.T. Yarch: None. **F. Federer:** None. **A. Angelucci:** None.

Poster

598. Identifying Circuits in Striate Cortex

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Topic: D.04. Vision

Support: Paul and Jody Allen

Title: Characterization of human and mouse neurons using an *in vitro* slice electrophysiology platform

Authors: *J. BERG, T. JARSKY, A. OLDRE, K. HADLEY, D. HILL, R. MANN, C. ANASTASSIOU, A. ARKHIPOV, T. CASPER, P. CHONG, N. DEE, D. FENG, K. GODFREY, N. GOUWENS, B. LEE,, L. LI, Y. LI, S. MIHALAS, L. NG, J. NYHUS, J. PERKINS, S. PARRY, D. REID, C. SLAUGHTERBECK, G. SOLER-LLAVINA, S. SULLIVAN, S. SUNKIN, N. TASKIN, C. TEETER, J. TING, C. FARRELL, M. HAWRYLYCZ, E. LEIN, J. W. PHILLIPS, C. KOCH, H. ZENG, A. BERNARD;
Allen Inst. For Brain Sci., Seattle, WA

Abstract: The Allen Institute has recently established the Allen Cell Types Database, with the goal of collecting electrophysiological, morphological, and transcriptional data from individual neurons of the mouse and human brain. An essential aspect of this database is the investigation of one of the most fundamental neuronal traits - intrinsic electrophysiological behavior. To compare the electrophysiological features of neurons that may contribute to cell classification, a standardized platform has been established for *in vitro* slice recording from mouse brain (with concurrent biocytin cell filling), followed by histological processing, imaging, and morphological reconstruction. Setting quality control parameters, standardized workflows, and increased automation allows for uniform data production across operator or electrophysiology rig. Data is gathered for each cell using a uniform set of electrophysiological stimuli to a) interrogate intrinsic membrane mechanisms that underlie the input/output function of neurons, b) infer aspects of neural response properties *in vivo* using *in vitro* data, and c) construct and test computational firing models, including detailed biophysical and generalized linear models, emulating the neuronal response to stereotyped stimuli. Thus far, the platform has been used to characterize hundreds of mouse neurons, data that are openly accessible via the Allen Brain Atlas web portal. In addition to the electrophysiological and morphological data acquired, each mouse neuron is registered within a common anatomical framework, or 3D reference atlas. The *in vitro* electrophysiology platform has also been applied to the analysis of live human brain slices derived from neurosurgeries at local hospital sites. Overlying neocortical resections are collected from individuals undergoing surgery for tumor removal or intractable epilepsy. By using standardized protocols and procedures, we aim to create a comprehensive, integrated database of cell type features for both human and mouse brain.

Disclosures: **J. Berg:** None. **T. Jarsky:** None. **A. Oldre:** None. **K. Hadley:** None. **D. Hill:** None. **R. Mann:** None. **C. Anastassiou:** None. **A. Arkhipov:** None. **T. Casper:** None. **P. Chong:** None. **N. Dee, D. Feng, K. Godfrey, N. Gouwens, B. Lee,:** None. **L. Li, Y. Li, S. Mihalas, L. Ng, J. Nyhus, J. Perkins:** None. **S. Parry, D. Reid, C. Slaughterbeck, G. Soler-Llavina:** None. **S. Sullivan, S. Sunkin, N. Taskin, C. Teeter, J. Ting:** None. **C. Farrell, M. Hawrylycz, E. Lein, J. W. Phillips:** None. **C. Koch, H. Zeng:** None. **A. Bernard:** None.

Poster

598. Identifying Circuits in Striate Cortex

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Topic: D.04. Vision

Title: Dendritic morphology feature analysis for mouse neuron classification

Authors: ***X. LIU**, S. SORENSEN, C. LEE, Z. ZHOU, B. LONG, S. SUNKIN, H. ZENG, M. HAWRYLYCZ, H. PENG;
Allen Inst. For Brain Sci., Seattle, WA

Abstract: Neuronal morphology characterization plays a crucial role in delineating neuronal cell types, as well as understanding neuronal function and connectivity. The Allen Cell Types Database currently contains more than one hundred 3D reconstructions of neuronal morphology generated from bright-field images of mouse neurons filled with biocytin during acute slice electrophysiology experiments. Here we present a study that extracts the most salient dendritic morphology features for distinguishing subtypes of neurons in mouse primary visual cortex. Twenty-one global morphological features were extracted from manually curated dendritic reconstructions. Both a supervised and an unsupervised strategy were deployed to explore neuron taxonomy. In the unsupervised approach, basic linear discriminant analysis was used to discover the hierarchical separations of neuron morphologies. In the supervised approach, neurons were first manually classified by neuroscientists into subgroups based on their shapes and their locations in the brain. We then used a machine learning method called MRMR (minimum redundancy and maximum relevance) to rank the features according to their saliency in terms of distinguishing those subtypes. K-fold cross validations were used to evaluate the classification results. The study provides insights in quantifying the morphological differences among neurons. Specific combinations of salient morphological features that correlate well with anatomical and functional clustering are revealed. The saliency ranks of the features are expected

to evolve as the Allen Cell Types Database grows both in number of samples and diversity of reconstructed neuronal morphologies.

Disclosures: **X. Liu:** None. **S. Sorensen:** None. **C. Lee:** None. **Z. Zhou:** None. **B. Long:** None. **S. Sunkin:** None. **H. Zeng:** None. **M. Hawrylycz:** None. **H. Peng:** None.

Poster

598. Identifying Circuits in Striate Cortex

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McDonnell Center for Systems Neuroscience

Title: Long range input to layer 1/2 drive distinct excitatory/inhibitory balance in modules within mouse primary visual cortex (V1)

Authors: *P. BISTA, A. BURKHALTER;
Anat. and Neurobio., Washington Univ. In St. Louis, Saint Louis, MO

Abstract: Layer 1 (L1) is a unique neocortical layer that is devoid of excitatory neurons, but contains a rich plexus of axons and axon terminals coming from subcortical sources such as thalamus and basal forebrain as well as feedback (FB) inputs from higher cortical areas (Dong et al., 2004; Wang et al., 2012). In addition, L1 contains apical dendrites of Pyramidal cells (Pyr) with cell bodies and basal dendrites in L2-6. Based on the highly polarized dendritic arbor and the stratification of inputs it has been proposed that L1 is an important node in which Pyr couple FB inputs to apical dendrites with FF inputs to basal dendrites in L3/4 (Larkum, 2013). Within the cerebral cortex, the vast majority of interareal FF and FB connections are formed by excitatory Pyr, which in the target area synapse onto Pyr and most often onto parvalbumin-expressing GABAergic interneurons (PV) (Gonchar and Burkhalter, 1999; 2003). In both pathways monosynaptic excitation of Pyr is followed by disynaptic PV-mediated inhibition, which is known as feedforward inhibition (Dong et al., 2004). More recently we have found that inputs from the dorsal lateral geniculate nucleus (dLGN) and several higher visual cortical areas to L1 of V1 terminate in patchy patterns. This raises the question whether inputs to Pyr and PV inside and outside the projection patches vary in absolute and relative strength. To study this

question, we used subcellular Channelrhodopsin-2 assisted circuit mapping (Petreanu et al., 2009) in acute tangential slices of mouse V1, in which PV neurons were genetically labeled with tdTomato. Whole cell patch clamp recordings showed that EPSCs recorded from L2/3 Pyr and PV aligned with patches that receive strong input from the dLGN were 2-3 times more powerful than outside projection patches. Similarly, EPSCs from Pyr and PV recorded inside patches with strong FB input were three times larger than outside patches, suggesting that input density scales with response strength. Inputs to PVs inside and outside of dLGN-projection patches were stronger than inputs to Pyr. A similar asymmetry was found in patches with weak FB input, suggesting that each of these inputs contacts subnetworks that are specialized for the selection of synchronous inputs and the filtering of noise. In contrast, inputs to Pyr and PV inside patches with strong FB projections were balanced. This suggests that activation of Pyr and PV in the same module is input-specific, tilted towards inhibition for dLGN input and similar for intracortical FB connections (Yang et al., 2013). The E/I ratio was balanced for FB input, a circuit mode known to broaden the integration window for coincident inputs and optimize sensory discrimination.

Disclosures: **P. Bista:** None. **A. Burkhalter:** None.

Poster

598. Identifying Circuits in Striate Cortex

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Program#/Poster#: 598.26/K22

Topic: D.04. Vision

Support: Paul G. Allen Family Foundation

Title: Linking electrophysiology and optophysiology *in vivo*

Authors: *P. LEDOCHOWITSCH[1], M. DUCROS[1], R. LIU[1], M. A. BUICE[1], C. MITELUT[1,2], C. ANASTASSIOU[1], P. SAGGAU[1], T. J. BLANCHE[1,3];
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Abstract: Single-unit recordings remain a core technology for *in vivo* electrophysiology. Yet, they offer only limited information about the location, morphology, or genotype of the recorded cells. Compared to traditional micro-wire electrodes, high-density silicon `polytrodes' improve single-unit isolation. Nonetheless, accurate, automated spike sorting remains a tremendous challenge, especially for high channel-count, contiguous electrode arrays. Ground truth data that

tie *in vivo* spike signals to the actual spiking neuron, crucial to validating spike sorting algorithms, are extremely difficult to acquire. On the other hand, ground truth data sets have been gathered through simultaneous polytrode recordings and patching of nearby cells in slice [Anastassiou et al, in press] and *in vivo* [Henze et al, 2001] yet this approach is impractical for an awake *in vivo* preparation where many cells contribute to the neural code as well as to the extracellularly recorded signals. In this work, we present viable and scalable alternatives. We combined high-density electrophysiology with multiphoton Ca^{2+} imaging, and single-cell optogenetics, to identify extracellular electrical signatures of specific neurons. We used high density silicon polytrodes with up to 900 recording sites spaced every 20 μm; resonant scanning, volumetric multiphoton imaging; a high-speed (>300 Hz) spatial light modulator (SLM) for single cell photo-stimulation and aberration correction, GCamP6f transgenic mice, and red-shifted channel rhodopsin derivatives (C1V1, ReaChR). We demonstrate and discuss spike detection and clustering in the presence of photovoltaic artifacts. We present strategies for establishing correspondence between extracellular action potentials and Ca^{2+} spikes. We further show that, with appropriate stimulation parameters, multiphoton-mediated photoactivation can occur in the absence of opsin expression. Our approach provides ground truth *in vivo* data for validating electrical and optical spike sorting algorithms, for optimizing the design of next generation polytrodes, and for quantifying the sampling biases inherent in extracellular recordings.

Disclosures: **P. Ledochowitsch:** None. **M. Ducros:** None. **R. Liu:** None. **M.A. Buice:** None. **C. Mitelut:** None. **C. Anastassiou:** None. **P. Saggau:** None. **T.J. Blanche:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); White Matter, LLC.

Poster

598. Identifying Circuits in Striate Cortex

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 598.27/K23

Topic: D.04. Vision

Title: Local connectivity of long-range projection neurons in mouse primary visual cortex

Authors: ***M. KIM**, M. IACARUSO, P. ZNAMENSKIY, T. MRSIC-FLOGEL;
Biozentrum, Univ. of Basel, Basel, Switzerland

Abstract: Cortico−cortical projections from mouse primary visual cortex (V1) to different higher visual areas convey distinct signals from the visual stimulus (Glickfeld et al., 2013).

However, it is not clear whether neurons projecting to the same target structure are preferentially interconnected, whereby they form functional subnetworks that process similar types of visual information. Here we investigate local synaptic connectivity and intrinsic membrane properties of layer (L) 2/3 and L5 V1 pyramidal cells projecting to either the anterolateral (AL) or the posteromedial (PM) cortical area, using multiple whole-cell patch-clamp recordings in brain slices targeted to neurons labelled with retrograde tracers (Cholera toxin B 488 and 594 injected in AL and PM respectively). We also characterize the visual response properties of these neurons with two−photon calcium imaging in anesthetized mice. We find that (i) AL and PM projection neurons in L2/3 preferentially receive local inputs from neurons projecting to the same long−range target, (ii) neurons projecting to both areas (i.e. double labelled with both retrograde tracers) are more frequent in L5 than in L2/3, (iii) double labelled neurons in L5 receive and provide more local connections than AL and PM projection neurons, (iv) AL projection neurons rarely receive synaptic inputs from other projection neurons in L5, (v) firing frequency of AL projection neurons by somatic current injection is higher than PM projection and double labelled neurons in L5, and (vi) functional tuning properties of these projection neurons in L2/3 are only slightly but significantly different under anaesthesia. Overall, our results indicate that local connectivity of long−range projection neurons in V1 are organized in a projection− and lamina−specific manner.

Disclosures: **M. Kim:** None. **M. Iacaruso:** None. **P. Znamenskiy:** None. **T. Mrsic-Flogel:** None.

Poster

598. Identifying Circuits in Striate Cortex

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Topic: D.04. Vision

Support: NSF-DMS grant #1122106

E.S.B. acknowledges funding from a Simons Fellowship in Mathematics, and the hospitality of the Allen Institute for Brain Science.

Title: Construction of a voxel based mesoscopic mouse connectome

Authors: K. D. HARRIS[1], J. HARRIS[2], H. ZENG[2], *S. MIHALAS[2], E. SHEA-BROWN[1]; [1]Applied Mathematics, Univ. of Washington, Seattle, WA; [2]Allen Inst. For Brain Sci., Seattle, WA

Abstract: Construction of a voxel based mesoscopic mouse connectome Kameron Decker Harris, Julie Harris, Hongkui Zeng, Stefan Mihalas, Eric Shea-Brown The long range connections between different areas in a mouse brain have been investigated using a hundreds of injections of an anterograde viral tracing followed by two photon tomographic imaging. For each experiment, injection sites are annotated both volumetric and by ontology, the images are segments and registered in 3D (Allen Connectivity Atlas). This establishes an injection based connectivity, which links the strength of connections to a particular position in the mouse brain from any of the areas which were included in the injection. In the past we used this information with two hypotheses: 1. that the signals sum linearly and 2. that the integral of the connections between different areas are independent of the exact position of the injection within the source region. This data was used to construct a mesoscopic whole brain connectome, which defines the connections between regions which can be as big as a few mm^3. However, the data are available at a finer scale: 100 μm voxel resolution. Our goal is to exploit this increased resolution by fitting a voxel-voxel connection weight matrix using these injection experiments. However, due to the large number of voxels compared to the number of injections, the problem is vastly underdetermined: the full voxel to voxel connectivity would have ~ 10^{12} degrees of freedom, while we are limited to $<10^3$ injections. Evidence from topographic maps suggests that some connection weights may vary smoothly in source and target position. We develop a way to regularize the underdetermined problem with a smoothness assumption and apply it to test data, and to evaluate the validity of this assumption. We pose the regularized inference as a convex optimization problem. This allows us to solve it efficiently for matrices with tens of millions of entries. The accuracy of the resulting weight matrix can be quantified via cross-validation, which also allows us to compare this spatial connectivity to the coarser regional connectivity. We start by applying these techniques to the visual areas. In our ongoing work, we hope to recover topographical correlates of stimuli (such as retinotopy) directly from connectivity as well as obtain a more detailed description of the mesoscale connectome. We also investigate parallel optimization methods which will allow us to solve for whole-brain connectivity matrices at O(100 μm) resolution.

Disclosures: K.D. Harris: None. **J. Harris:** None. **H. Zeng:** None. **S. Mihalas:** None. **E. Shea-Brown:** None.

Poster

599. Striate Cortex Plasticity

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Topic: D.04. Vision

Support: NIH 5-R01-EY011894-17

Title: Mechanisms of experience dependent synaptic stabilization in layerII/III excitatory neurons in mouse visual cortex

Authors: *J. SUBRAMANIAN, A. BALCIOGLU-DUTTON, E. NEDIVI;
Picower Inst. for Learning and Memory, MIT, Cambridge, MA

Abstract: Changes in sensory experience lead to formation of new synapses and elimination of some pre-existing synapses in corresponding sensory cortices. Excitatory synapse formation is thought to be a multistep process that involves exploratory protrusion of new dendritic spines followed by spine retraction or by recruitment of synaptic proteins and spine stabilization. Conversely, excitatory synapse elimination potentially involves initial synaptic loss, followed by spine retraction. Unfortunately, delineating these steps and their underlying molecular mechanisms *in vivo* has been hampered by the need to independently label the dendritic spine separately from the synapse, and to chronically follow their dynamics at high temporal resolution. Further, how experience drives formation and stabilization of new synapses remains poorly understood. By combining *in utero* electroporation, cranial window implantation and multi-color two-photon microscopy, we were able to simultaneously track the fate of dendritic spines and their synapses in individual layer II/III neurons in mouse visual cortex. We find that excitatory synapse formation and stabilization is a protracted process that occurs over a period of days. Only a small fraction of newly formed spines recruit PSD95, an excitatory post synaptic density protein, and the presence of PSD95 correlates with their stabilization. To gain molecular insight into synapse formation/stabilization, we tested for participation of CPG15, a small protein indirectly implicated in synaptic stabilization and expressed in visual cortex in response to visual experience, by comparing steps in synapse formation in wild type (WT) versus CPG15 knock out (KO) mice. We found that new spine protrusions are similarly initiated in WT and KO animals. However, in the KO mice, newly formed spines were not able to recruit PSD95 and were lost as a consequence. Interestingly, the deficit in excitatory synaptic remodeling in KO mice is dependent on the animals' light experience. In total darkness, where CPG15 expression is down regulated in WT mice, synaptic dynamics were similar between the two genotypes. Our prior studies have shown that inhibitory synapses can also be formed on dendritic spines. To test whether CPG15 regulate inhibitory synapses, we also tracked the dynamics of Gephyrin, a post synaptic protein at inhibitory synapses. In contrast to excitatory synapses, inhibitory synaptic remodeling is not affected by CPG15, thereby, demonstrating distinct molecular requirements for these two processes. Thus, we propose that CPG15 could selectively stabilize excitatory synapses that are active during experience-dependent plasticity.

Disclosures: J. Subramanian: None. **A. Balcioglu-Dutton:** None. **E. Nedivi:** None.

Poster

599. Striate Cortex Plasticity

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Title: Correlated turnover of inhibitory boutons during ocular dominance plasticity

Authors: *R. RAJENDRAN, H. SAIEPOUR, A. J. HEIMEL, C. N. LEVELT;
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Abstract: Inhibitory neurotransmission has been suggested to play a major role in adult cortical plasticity. Studies from our lab and others demonstrated that inhibitory synapses on apical tufts of layer 2/3 pyramidal neurons show an increased turnover during ocular dominance (OD) plasticity (van Versendaal et al., 2012, Chen et al, 2012), while this is not the case with excitatory synapses (Hofer et al., 2009). However, it is unclear which inhibitory neuron subtype provides input to these plastic synapses. Parvalbumin (PV) neurons have been strongly implicated in ocular dominance plasticity, and reduction of PV inhibition results in increased plasticity in various brain regions (Kuhlman et al., 2013, Donato et al., 2013). On the other hand studies using optogenetic techniques have shown that Somatostatin (SST) and Vasoactive intestinal polypeptide (VIP) interneurons are necessary and sufficient for adult OD plasticity (Fu et al., 2015). More recently, transplantation of medial ganglionic eminence, which consists of PV and SST but not VIP interneuron populations, in adult visual cortex, reinstates OD plasticity (Davis et al., 2015). While VIP neurons mostly innervate other interneurons, PV and SST interneurons are known to provide dense innervation to layer 2/3 pyramidal neurons. We therefore considered PV and SST as possible candidates to test which interneuron subtype provides inputs to the plastic cohort of inhibitory synapses, on layer 2/3 pyramidal neurons (van Versendaal et al., 2012). PV or SST neurons in binocular primary visual cortex of mice are labeled with GFP, using a viral vector, and labeled boutons imaged through a cranial glass window, using *in vivo* 2-photon imaging. Imaging sessions are repeated every 4 days during baseline, monocular deprivation and recovery (van Versendaal et al., 2012). Boutons are tracked

through all time points and percent turnover rate was determined. We will present data showing how the turnover of boutons from PV- or SST-expressing interneurons correlates with the turnover of inhibitory synapses on layer 2/3 pyramidal neurons during OD plasticity.

Disclosures: R. Rajendran: None. **H. Saiepour:** None. **A.J. Heimel:** None. **C.N. Levelt:** None.

Poster

599. Striate Cortex Plasticity

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Topic: D.04. Vision

Support: IWT fellowship to IS

FWO Flanders Research Grant

IWT-SBO Research Grant

Title: Optogenetic interference with somatostatin-interneuron activity suppresses enucleation-induced cross-modal plasticity in the adult mouse visual cortex

Authors: *I. SCHEYLTJENS[1], S. VREYSEN[1], M.-E. LARAMÉE[1], E. DREESEN[1], C. VAN DEN HAUTE[2], V. BAEKELANDT[2], J. NYS[1], L. ARCKENS[1];
[1]Biol., [2]Neurosci., KU Leuven, Leuven, Belgium

Abstract: The visual cortex of adult mice retains the ability to recover upon deactivation after monocular enucleation (ME). Open eye potentiation induces an early but restricted reactivation, leading to the expansion of the binocular zone into monocular territory. The slower and larger impact of cross-modal plasticity facilitates reactivation of the medial monocular cortex by whisker-related inputs (Van Brussel et al., 2011). A dark exposure (DE) period of 10 days prior to ME specifically prevents the late cross-modal reactivation. DE affects GABAergic synaptic transmission differently in binocular and monocular V1, showing that intracortical inhibition is an important regulator of the cross-modal response to unilateral visual deprivation (Huang et al., 2010; Nys et al., in revision). The subpopulation of somatostatin (SOM)-expressing inhibitory interneurons has the potential to play a role in regulating this cross-modal plasticity. These cells do not receive thalamic input and are widespread in infragranular layers where the cross-modal component has a maximal influence in the visual cortex upon loss of the dominant sensory input (Iurilli et al., 2012; Markram et al., 2004; Urban-Ciecko et al., 2015, Van Brussel et al, 2011).

Localized optogenetic SOM-interneuron activation in V1/V2M upon Cre-dependent rAAV2/7 driven stable-step function opsin (SSFO) transduction was performed on 3 consecutive days, prior to ME, combined or not with DE pretreatment. Successful activation/deactivation of the SSFOs by blue/yellow laser pulses was verified by means of extracellular multi-unit recordings. The limitation or potentiation of plasticity by optogenetic stimulation of SOM-interneurons was determined by charting the expression levels of the activity marker zif268. The modulation of SOM-interneurons hampered cross-modal plasticity in all conditions. These observations identify the SOM-interneuron population as an essential cellular component and call for future investigations aiming at elucidating how SOM-specific inhibitory mechanisms direct cross-modal plasticity in adulthood.

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Poster

599. Striate Cortex Plasticity

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Topic: D.04. Vision

Support: NIH Grant R01-Ey017656-06A1

Title: Daily *in vivo* imaging of inhibitory and excitatory synapses during the progression of an ocular dominance shift

Authors: *K. P. BERRY[1], K. VILLA[1], J. SUBRAMANIAN[1], J. CHA[1], P. T. C. SO[1], Y. KUBOTA[2], E. NEDIVI[1];
[1]MIT, Cambridge, MA; [2]Natl. Inst. for Physiological Sci., Okazaki, Japan

Abstract: The capacity for dynamic adaptations in response to environmental changes is a key mechanism mediating neuronal plasticity. Inhibitory neurons are known to play a vital role in defining the window for critical period plasticity during development, and it is increasingly apparent that they continue to exert powerful control over experience dependent cortical plasticity in adulthood. During normal visual experience, inhibitory dendrites and synapses are highly dynamic in the binocular visual cortex of the mouse. Monocular deprivation (MD), which induces an ocular dominance (OD) shift, significantly increases the elimination of inhibitory synapses. In contrast, the dynamics of spines, assumed to be a morphological surrogate for excitatory synapses, are not significantly altered after MD on layer II/III pyramidal neurons.

However, after a MD there is a greater likelihood that dynamic spines and inhibitory synapses will occur near each other. This clustering of dynamic events suggests that a subpopulation of dynamic spines may be preferentially affected and is hidden within the larger population of dynamic spines, which as a whole does not appear to be significantly altered by MD. To determine if such a population exists as well as to dissect the progression of an OD shift in greater detail, we utilized a three-color labeling strategy in conjunction with spectrally resolved two-photon microscopy to image all the excitatory and inhibitory postsynaptic sites on individual neurons in the binocular visual cortex of living mice. Daily imaging of the same neurons reveals the structural dynamics of both excitatory synapses, labeled with PSD-95-mCherry, and inhibitory synapses, labeled with teal-gephyrin. We find that under normal visual experience, the majority of dynamic spines lack PSD-95 during daily imaging. With the ability to discern between dynamic spines that do or do not carry an excitatory synapse, we now examine excitatory and inhibitory synapse dynamics and their spatial relations during the progression of an OD shift with high temporal resolution.

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Poster

599. Striate Cortex Plasticity

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: D.04. Vision

Support: NIH Grant EY016431

Title: Temporal frequency-dependent potentiation of visually-evoked responses in adult mouse visual cortex

Authors: *C. L. LANTZ, E. M. QUINLAN;
Dept. of Biol., Univ. of Maryland, College Park, MD

Abstract: Repeated visual presentation of sinusoidal gratings induces robust stimulus-selective response potentiation of visually evoked potentials (VEPs) in layer 4 of mouse visual cortex (Cooke, Bear, 2010). Here we use this robust form of experience-dependent synaptic plasticity to survey the plasticity available to different classes of neurons across layers of the visual cortex. Chronically implanted electrode arrays were used to acquire VEPs and single units across all cortical layers in awake adult C57 mice. Visual stimuli (high contrast, low spatial frequency

sinusoidal gratings) reversing at 1 Hz induced an increase in the visually-evoked firing rates in fast spiking inhibitory neurons in layer IV (FS IN; percent change 148 ± 53%) and in regular spiking (RS) neurons in all layers (percent change; layer II/III, 85 ± 23%; layer IV, 109 ± 30%; layer V, 93 ± 43%). However, an increase in the VEP amplitude was observed in layer IV (percent change; 19.2 ± 3 %) and V (17.5 ± 6%) but not layer II/III (1.4 ± 4%). Thus the source of increased neuronal excitability following repetitive visual stimulation at 1 Hz differs across cortical layers. Reversible pharmacological silencing of cortical spiking confirmed an increase in the thalamocortical contribution to the VEP (percent change, layer IV, 32 ± 5%; layer V, 12 ± 5%), and an increase in the corticortical contribution to the VEP in extragranular layers (11.3 ± 5%). In contrast, visual stimuli presented at 10 Hz induced a decrease in visually-evoked firing rates of RS neurons across cortical layers (percent change; layer II/III, -60 ± 5%; layer IV, -39 ± 10%; layer V, -50 ± 15%) and no change in excitability of layer IV FS INs (29 ± 72%). However, VEP amplitudes were increased throughout the visual cortex (layer II/III, 38 ± 12%; layer IV, 43 ± 6%; layer V, 53 ± 19%). This suggests that 10 Hz visual stimulation recruits mechanisms of firing rate homeostasis that are not dependent on enhancing excitability of FS INs. Indeed, NARP-/- mice, which have a deficit in the recruitment of inhibition from FS INs due to reduced excitatory drive, express potentiation of VEP amplitudes in response to 10 Hz but not 1 Hz visual stimulation.

Disclosures: **C.L. Lantz:** None. **E.M. Quinlan:** None.

Poster

599. Striate Cortex Plasticity

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Topic: D.04. Vision

Support: NHMRC Grant 525459

Title: Sensory experience modifies the spatial relationship between orientation and ocular dominance maps in visual cortex

Authors: S. L. CLOHERTY[1], N. J. HUGHES[2], G. J. GOODHILL[2], *M. R. IBBOTSON[1]; [1]Natl. Vision Res. Inst., Melbourne, Australia; [2]Queensland Brain Inst., Univ. of Queensland, Brisbane, Australia

Abstract: Brain structure is influenced by sensory inputs during development and much has been gained by investigating this topic in the mammalian visual cortex. Maps of orientation

preference (OP) and ocular dominance (OD) in the primary visual cortex can be readily manipulated by rearing animals in environments with restricted visual input (e.g. stripe rearing or monocular deprivation). However, in all previous experiments of this type the spatial relationship between OP and OD maps has appeared fixed. However, computational models for map formation based on 'dimension-reduction' predict that the relationship between OP and OD maps is sensitive to visual experience. We have shown that indeed this relationship can be modified by altered visual experience. We reared cats wearing cylindrical lenses over both eyes for 6 hours per day (otherwise in the dark), biasing input in one eye towards vertical orientations, and in the other eye towards horizontal orientations. By doing this we were able to manipulate both the OP and OD maps simultaneously. After ~5 months of rearing we used intrinsic signal optical imaging to measure OP and OD maps in primary visual cortex and compared them to maps from cats reared without lenses (subject to the same light-dark cycle). In our normally-reared cats OP pinwheel centres were most often located in the middle of OD columns, as reported previously. However, in our cross-reared animals we observed a significant shift of OP pinwheel centres away from the middle of OD columns. The shift in OP pinwheels that we observed in our cross-reared animals is well predicted by a computational model for map formation based on dimension reduction. Our results reveal a previously unknown degree of brain plasticity in response to altered sensory input and provide further evidence that the principle of dimension reduction captures essential elements of the mechanisms by which cortical maps develop.

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Poster

599. Striate Cortex Plasticity

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Topic: D.04. Vision

Support: PhD fellowship IWT Flanders to KS

KU Leuven Research Council GOA grant

Title: A new effective cell surface proteomics approach for mm3-tissue samples to investigate cross-modal plasticity in mouse visual cortex

Authors: *L. H. ARCKENS[1], N. LOMBAERT[1], J. NYS[1], D. VALKENBORG[2], G. BAGGERMAN[2], K. SMOLDERS[1];
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Abstract: The contralateral visual cortex of adult mice reactivates completely upon monocular enucleation (ME) due to a combination of consecutive visual and cross-modal plasticity processes (Van Brussel et al., 2011). However, this response is age-dependent. Adolescent mice clearly lack the late recruitment of cross-modal plasticity mechanisms and therefore fail to fully recover from ME (Nys et al., 2014). A recent 2-D DIGE screen suggested a critical role for cytoskeletal changes. Yet, the importance of plasma membrane proteins (PMPs) like (G-protein coupled) receptors, ion channels and transporters cannot be judged by this in-gel proteomics approach. Here we report a new workflow where biotinylation of acute tissue slices and streptavidin pulldown from mm3-scale tissue is followed by shotgun proteomics. It allowed the selective extraction and identification of >1,600 proteins of which more than 60% is reported to be associated to the plasma membrane. This new approach convincingly outcompetes the traditional approach of PMP extraction by ultracentrifugation, suffering from poor extraction efficiency and high sample consumption. Furthermore, we delivered proof-of concept for neurobiology research that our method allows focusing on PMP proteins located at the synapse, in neuronal projections and in dendritic spines. Upon enrichment, subjecting the samples to a gel-free differential TMT mass spectrometry screening provides a more complete view on the signaling cascades regulating the age factor for cross-modal plasticity. We believe that many research fields outside neuroscience, including cancer, immunology and stem cell research will also greatly benefit from our new plasma membrane proteomics research approach.

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Poster

599. Striate Cortex Plasticity

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Topic: D.04. Vision

Support: NIMH Silvio Conte Center 1P50MH094271

Title: Experience-dependent miR-34a triggers critical period plasticity by repressing GAT1

Authors: *Y. KOBAYASHI[1,2], M. D. CAIATI[1], T. K. HENSCH[1,2];
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Abstract: Controlling GABAergic transmission is pivotal for inducing critical period plasticity, but the underlying molecular mechanisms remain elusive. Here, we show that miR-34a, an experience-dependent microRNA, triggers visual cortical (V1) plasticity by directly repressing the major GABA transporter, GAT1. In mouse V1, miR-34a emerged gradually after eye-opening predominantly in the inhibitory parvalbumin (PV) positive-cells. Dark-rearing delayed this developmental increase concomitant with a post-transcriptional up-regulation of GAT1. Mechanistically, miR-34a directly repressed GAT1 expression through the 3' untranslated region of GAT1 mRNA (Slc6a1). Conditional deletion of miR-34a within PV-cells decreased tonic inhibition in pyramidal cells and accelerated the decay constant of evoked IPSCs, consistent with an elevated expression of presynaptic GAT1. Finally, brief monocular deprivation revealed a lack of visual plasticity at the typical critical period peak (P24-28) in the miR-34a conditional knock-out mice, which was rescued by administration of a selective GAT1 inhibitor, NO711. These data demonstrate a developmental role for the miR-34a/GAT1 axis within PV-cell circuits to optimally delay critical period onset by regulating extracellular GABA levels.

Disclosures: Y. Kobayashi: None. **M.D. Caiati:** None. **T.K. Hensch:** None.

Poster

599. Striate Cortex Plasticity

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Uehara memorial Foundation

Title: Lynx1 limits dendritic spine turnover in adult visual cortex

Authors: *M. SAJO[1,2,3], G. C. R. ELLIS-DAVIES[2], H. MORISHITA[1,2,3];
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Abstract: Cortical plasticity is limited after the developmental critical period. This in turn limits recovery from brain disorders and injuries in adults. Identification of the mechanisms that regulate developmental decline in plasticity not only at functional but also at structural level would provide promising targets for robust recovery. In mouse visual cortex (V1), a well-established model of cortical plasticity, it is known that adult wild-type (WT) mice require 4 days of monocular deprivation to elevate the spine gain rate in layer 5 pyramidal neurons (Hofer et al 2009). However, no change was induced in spine loss rate, a juvenile signature of plasticity. Lynx1, an endogenous inhibitor for nicotinic acetylcholine receptors, was recently identified to limit juvenile-like experience-dependent functional plasticity in the adult V1. We hypothesized that the robust juvenile-like spine turnover is masked by the increased expression of Lynx1 in adults. To test this, the spine turnover rate in adult V1 of Lynx1 knock-out (KO) mice was measured by *in vivo* chronic imaging using two-photon microscopy. Dendrites from layer 5 pyramidal neurons were sparsely labeled by mating Lynx1KO mice with Thy1-GFP M line mice. Cranial windows were chronically implanted over the visual cortex. Dendrites in layer 1 of male mice were subjected to longitudinal fluorescent imaging every 4 days before and after monocular deprivation. We found that, in the adult Lynx1KO mice, the baseline spine gain rate was already higher than that of adult WT mice without deprivation, and comparable to the elevated rate in deprived adult WT mice. This spine gain rate remained high after 4 days of deprivation. Strikingly, spine loss rate was also elevated in Lynx1KO mice at the baseline level and remained higher after the deprivation compared to WT matched controls. Collectively, the removal of Lynx1 is not only sufficient to unmask robust spine gain without additional visual deprivation, but also allows an increase in spine loss before and during monocular deprivation. Our data point to the key role of Lynx1 in masking juvenile form of structural plasticity through its action on spine turnover.

Disclosures: **M. Sajo:** None. **G.C.R. Ellis-Davies:** None. **H. Morishita:** None.

Poster

599. Striate Cortex Plasticity

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Support: NIH Grant 1R01EY021580

Title: Regulation of experience-dependent plasticity in visual cortex following ngr1 deletion within individual cortical layers

Authors: *M. G. FRANTZ[1,2], A. W. MCGEE[3];
[1]Michael Frantz, Los Angeles, CA; [2]Neurosci. Grad. Program, [3]Saban Res. Inst., USC, Los Angeles, CA

Abstract: The neural circuits of cerebral cortex are most sensitive to modification by experience during developmental critical periods. Yet how the duration and closure of critical periods are regulated remains poorly understood. Within the critical period for ocular dominance (OD) plasticity, but not thereafter, a brief four-day monocular deprivation (MD) results in saturating shifts in responses of single units in mouse binocular visual cortex towards the nondeprived eye. However, mice lacking the nogo-66 receptor gene (ngr1) retain this plasticity as adults. How ngr1 contributes to closing this critical period is unclear. To explore the neuronal expression requirements for ngr1 to limit OD plasticity within adult visual cortex, we are characterizing the effects of 4-day MD of adult mice in which we have deleted the ngr1 gene in subsets of cortical neurons by combining a conditional 'floxed' mutant of ngr1 (flx) with one of several driver lines for Cre recombinase. Deleting ngr1 in cortical excitatory neurons with the CamK2a-Cre transgene permits OD plasticity at postnatal day 60 (P60) indistinguishable from the constitutive ngr1 KO mouse. In on-going experiments, we are examining whether ngr1 expression is required by excitatory neurons in one or more layers of cortex to close this critical period. These experiments will improve understanding of where ngr1 operates within visual cortex to close the critical period and how OD plasticity is coordinated between cortical layers.

Disclosures: **M.G. Frantz:** None. **A.W. McGee:** None.

Poster

599. Striate Cortex Plasticity

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 599.11/K35

Topic: D.04. Vision

Support: NIH Grant EY016431

Title: Bidirectional regulation of matrix metalloproteinase-9 (mmp-9) activity by visual experience in the adult mouse primary visual cortex

Authors: *S. MURASE, Y. GU, E. M. QUINLAN;
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Abstract: MMP-9, an extracellular zinc-dependent endopeptidase, participates in the activity-dependent remodeling of dendritic structure by degrading components of the extracellular matrix (ECM). We have recently shown that MMP-9 has widespread impact on cortical circuit development, including the regulation of neuronal morphology, synaptic connectivity and excitability. Degradation of the ECM by MMP-9 has also been implicated in the potentiation of excitatory synapse structure and function in the juvenile hippocampus and visual cortex. Structural and functional plasticity are significantly constrained over the course of postnatal development in the mammalian cortex. However, binocular visual deprivation through dark exposure (DE) reactivates synaptic plasticity in the primary visual cortex (V1) of adult rodents, promoting the structural and functional recovery from severe amblyopia. Here we show that the expression and activity of MMP-9 is bidirectionally regulated in adult mouse V1 by visual experience. Dark exposure in adulthood decreases the expression (34±5.6%) and activity (cleavage of β-dystroglycan 40±7.3%) of MMP-9. Subsequent brief exposure (2 hr) to a normal lighted environment (DEL) induces a rapid recovery of MMP-9 expression (115±7.9%) and an increase in MMP-9 activity (317.8±50.4%). Reduction of excitability in dark-exposed V1 with diazepam, an allosteric modulator of ligand-bound $GABA_A$ receptors, which inhibits the rescue of ocular dominance plasticity, decreased the expression and activity of MMP-9 (41±5.1% and 31±11.5%) and blocked the bidirectional regulation of MMP-9 by visual experience. In contrast, treatment of $NARP^{-/-}$ mice with diazepam, which rescues ocular dominance plasticity, enabled the bidirectional regulation of MMP-9 expression and activity by visual experience. Importantly, *in vivo* zymography for MMP-9 activity colocalized with markers for excitatory synapses (VGluT1, 61.2±5.3%; VGluT2, 43±3.3%), and synaptic MMP-9 activity was reduced by DE (63.2±6.1%) and enhanced by DEL (133.6±10.6%). These data support a model in which synapse-specific degradation of ECM is activated by visual experience following DE, which may participate in experience-dependent recovery of structure and function in dark-exposed amblyopes. Supported by NINDS/NIH intramural Research Program and R01EY016431.

Disclosures: S. Murase: None. **Y. Gu:** None. **E.M. Quinlan:** None.

Poster

599. Striate Cortex Plasticity

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Deutsche Forschungsgemeinschaft through the Collaborative Research Center 889 "Cellular Mechanisms of Sensory Processing" (Project B5) (SL)

Title: Environmental enrichment preserves lifelong ocular dominance plasticity in mouse visual cortex

Authors: *F. GREIFZU, S. LÖWEL;
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Abstract: Ocular dominance (OD) plasticity in the primary visual cortex (V1) of standard cage raised mice declines during postnatal development and is absent beyond postnatal day (PD) 110 (Lehmann & Löwel, 2008, PLoS ONE). Using *in vivo* optical imaging of intrinsic signals we have shown that raising mice in an enriched environment (EE) can extend the sensitive phase for OD-plasticity up to PD196 (Greifzu et al., 2014, PNAS). This preserved OD-shift was juvenile-like as it was mediated by reductions in deprived eye responses in V1. Whether EE can preserve OD-plasticity throughout life and if it is continuously the juvenile type of OD-plasticity is not yet known. We therefore raised mice in EE until >PD400 or >PD700 and examined them for OD-plasticity. Indeed, 7 days of MD induced an OD-shift in EE-mice until at least PD809 (oldest mouse tested). In EE-mice >PD400/>PD700, the ODI decreased from 0.25±0.02 (n=5) before MD to 0.07±0.03/0.01±0.04 (n=6/4) after MD ($P<0.01$ for both groups, t-test). In contrast to the younger EE-mice, which showed a juvenile-like OD-plasticity, the old EE-mice displayed an adult OD-shift, mediated by increases in open eye responses in V1. In addition, EE housing could also restore OD-plasticity in standard cage mice which are beyond the sensitive phase for OD-plasticity: transferring mice from standard cages to EE at PD110 allowed OD-plasticity after MD in animals until at least PD922. Taken together, EE preserves lifelong OD-plasticity. In EE-mice around PD200, OD-shifts are mediated by reductions in deprived eye responses (juvenile-like OD-shift), while OD-shifts in EE-mice older than PD400 are mediated by increases in open eye responses in V1 (adult OD-shift). Since in standard cage raised mice, juvenile OD-plasticity is limited to the critical period, which ends around PD40, our results suggest that EE-raising prolongs juvenile OD-plasticity by a factor of about 10 (PD40 vs. PD400).

Disclosures: F. Greifzu: None. **S. Löwel:** None.

Poster

599. Striate Cortex Plasticity

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Topic: D.04. Vision

Support: CONICET PIP 112 200901 00738

UNC 06/C379

Title: Effect of synaptic plasticity on orientation selectivity in the primary visual cortex

Authors: *G. MATO[1], S. GONZALO COGNO[2];
[1]CNEA and CONICET, Bariloche, Argentina; [2]Inst. Balseiro, Bariloche, Argentina

Abstract: Orientation selectivity is ubiquitous in the primary visual cortex (V1) of mammals. In cats and monkeys, V1 displays spatially ordered maps of orientation preference. Instead, in mice, squirrels and rats, orientation selective neurons in V1 are not spatially organized, giving rise to a seemingly random pattern usually referred to as a salt-and-pepper layout. The fact that such different organizations can sharpen orientation tuning leads to question the structural role of the intracortical connections; specifically the influence of plasticity and the generation of functional connectivity. In this work, we analyse the effect of plasticity processes on orientation selectivity for both scenarios. We study a computational model of layer 2/3 and a reduced one-dimensional model of orientation selective neurons, both in the balanced state. We analyse two plasticity mechanisms. The first one involves spike-timing dependent plasticity (STDP), and the second one the reconnection of the interactions according to the preferred orientations of the neurons; this last rule gives rise to functional connectivity. We find that under certain conditions STDP can indeed improve selectivity but it works in a somehow unexpected way, that is, effectively decreasing the modulated part of the intracortical connectivity as compared to the non-modulated part. The degree of functional connectivity generated by the plasticity process depends on the selectivity in the initial condition. As in the balanced state the degree of selectivity is inversely proportional to the functional connectivity we have a self stabilizing process that tends to a fixed value of selectivity in the final state. For the reconnection mechanism we also find that increasing functional connectivity leads in fact to a decrease in orientation selectivity if the network is in a stable balanced state. Both counterintuitive results are a consequence of the dynamics of the balanced state. We also find that selectivity can be increased by a reconnection process if the resulting connections give rise to an unstable balanced state for a given Fourier mode. We compare these findings with recent experimental results.

Disclosures: G. Mato: None. **S. Gonzalo Cogno:** None.

Poster

599. Striate Cortex Plasticity

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Topic: D.04. Vision

Support: NIH Fellowship F31 AG044061-03

NIH Grant R01-EY017656-06A1

Title: Inhibitory synapses are repeatedly assembled and removed at persistent sites *in vivo*

Authors: *K. L. VILLA[1], K. P. BERRY[1], J. SUBRAMANIAN[1], J. CHA[1], P. T. C. SO[1], Y. KUBOTA[2], E. NEDIVI[1];
[1]MIT, Cambridge, MA; [2]Natl. Inst. for Physiological Sci., Okazaki, Japan

Abstract: Brain plasticity allows neural networks to dynamically adapt in response to the environment by remodeling connections between neurons. Recent *in vivo* imaging studies have overturned the idea that adult brains are hard-wired, by demonstrating the capacity for structural remodeling of spines and synapses. Such remodeling events are commonly thought to mediate rearrangements in microcircuit connectivity. Using three-color labeling and spectrally resolved two-photon microscopy, we simultaneously tracked *in vivo* the structural dynamics of all excitatory and inhibitory postsynaptic sites on individual neurons in mouse neocortex, using PSD-95-mCherry and teal-gephyrin as markers of excitatory and inhibitory synapses, respectively. We found that on a daily basis inhibitory synapses on dendritic spines are exceptionally dynamic, largely because many of them disappear and reappear in the same location. In contrast, excitatory synapses on the same spines (dually innervated spines) are extremely stable. We performed post-hoc electron microscopy on dendritic segments which had been imaged for 9 days *in vivo* and found that in some cases, an inhibitory axon can be found at the location of a recently disappeared inhibitory synapse, suggesting that the axon may serve as a placeholder for the rapid reformation of the inhibitory synapse. This reversible type of synapse structural dynamics indicates a fundamentally new role for inhibitory synaptic remodeling - flexible, input-specific gating of stable excitatory connections.

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Poster

599. Striate Cortex Plasticity

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Support: Mary-Rita Angelo Fellowship (AJS)

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Big Ideas Generator at the University of Chicago (SEP, JNM)

NSF CAREER (JNM)

Title: Effective compression of predictive information in retinal ganglion cells learned through STDP

Authors: *A. SEDERBERG[1,2,3], J. N. MACLEAN[2,4], S. E. PALMER[3,4];
[2]Neurobio., [3]Organismal Biol. and Anat., [4]Committee on Computat. Neurosci., [1]Univ. of Chicago, Chicago, IL

Abstract: Prediction is necessary for the brain to overcome delays incurred by sensory processing. A recent study by Palmer et al. (PNAS, 2015) revealed that prediction happens early in visual processing, starting in the retina. This predictive information was highly compressible: a single binary output function could capture nearly all of the predictive information carried by a group of cells. In principle, there are very many (2^(2^N)) ways to partition the 2^N binary states of N neurons into one binary output, and the optimal output rule for compressing predictive information could be any of these. The fact that a perceptron, which can implement a tiny fraction of the total possible rules, achieves near optimal representation of the predictive information in the inputs is surprising. This also suggests that using this predictive information downstream of the retina is biologically plausible. Here, we also show that these near-optimal perceptron rules are learnable. We investigate whether this compression can be learned using spike-timing-dependent plasticity (STDP). In the first part of our study, we demonstrate that STDP can learn predictive rules from model data generated by a Markov process with a structured transition matrix, provided the matrix does not correspond to an exclusive-OR-like operation on the inputs. Eliminating temporal structure of input data during the training period diminishes the similarity between the learned perceptron and the optimal perceptron. In the second part of the study, we use data from retinal recordings as the input and demonstrate the efficacy of STDP for learning the optimally predictive output rule. Networks trained with data generated during the playback of a natural movie capture most of the available predictive information.

Disclosures: A. Sederberg: None. **J.N. MacLean:** None. **S.E. Palmer:** None.

Poster

599. Striate Cortex Plasticity

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Topic: D.04. Vision

Support: NIH Grant EY021580

Pre-doctoral fellowship from the Saban Research Institute, Children's Hospital Los Angeles

Title: Plasticity of binocularity and visual acuity are differentially limited by nogo receptor

Authors: *C.-E. STEPHANY[1], L. L. H. CHAN[2], H. H. M. DORTON[1], S. N. PARIVASH[1], S. QIU[3], A. W. MCGEE[1];
[1]Saban Res. Institute, Children's Hosp. Los Angeles, Los Angeles, CA; [2]Dept. of Electronic Engin., City Univ. of Hong Kong, Hong Kong, China; [3]Dept. of Basic Med. Sci., Univ. of Arizona Col. of Med., Phoenix, AZ

Abstract: The closure of developmental critical periods consolidates neural circuitry but also limits recovery from early abnormal sensory experience. Degrading vision by one eye throughout a critical period both perturbs ocular dominance (OD) in primary visual cortex and impairs visual acuity permanently. Yet understanding how binocularity and visual acuity interrelate has proven elusive. Here we demonstrate the plasticity of binocularity and acuity are separable, and differentially regulated by the neuronal nogo receptor 1 (NgR1). Mice lacking NgR1 display developmental OD plasticity as adults. Furthermore, their visual acuity and OD spontaneously recover after prolonged monocular deprivation throughout the critical period. Restricting deletion of NgR1 to either cortical interneurons or a subclass of parvalbumin-positive interneurons alters interlaminar synaptic connectivity in visual cortex and prevents closure of the critical period for OD plasticity. However, loss of NgR1 in PV neurons does not rescue deficits in acuity induced by chronic visual deprivation. Thus, NgR1 functions with PV interneurons to limit plasticity of binocularity, but its expression is required more extensively within brain circuitry to limit improvement of visual acuity following chronic deprivation.

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Poster

599. Striate Cortex Plasticity

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Topic: D.04. Vision

Support: NSERC

Title: Understanding the role of fluoxetine in reinstating critical period-like plasticity

Authors: *S. BESHARA[1], J. G. A. PINTO[1], D. G. JONES[3], K. M. MURPHY[1,2];
[1]McMaster Integrative Neurosci. Discovery and Study, [2]Psychology, Neurosci. & Behavior, McMaster Univ., Hamilton, ON, Canada; [3]Pairwise Affinity Inc, Dundas, ON, Canada

Abstract: Fluoxetine has emerged as a novel pharmaceutical therapy for amblyopia because it reinstates critical period-like plasticity and promotes total recovery of visual acuity in adult animals. Translating these results from animal models to clinical therapies, however, has been challenging because of the lack of mechanistic understanding. For example, shifts in the physiological excitatory/inhibitory (E/I) balance are necessary to open and maintain the critical period, but fluoxetine's impact on the E/I balance remains unclear: Fluoxetine reduces intracortical concentrations of the inhibitory neurotransmitter GABA, but it increases the expression of genes associated with inhibitory transmission. Because gene and protein expression are only weakly correlated, we do not know if fluoxetine affects the expression of synaptic proteins that determine the E/I balance and the potential for plasticity. Here, we studied the effect of fluoxetine treatment in adult rats, alone or in combination with visual deprivation (monocular deprivation, MD), on a set of highly conserved pre- and post-synaptic proteins (Synapsin, Synaptophysin, PSD-95, Gephyrin). Synapsin and Synaptophysin contribute to exo- and endo-cytosis of neurotransmitter vesicles, respectively, and support normal patterns of neural firing by affecting neurotransmitter release. The glutamatergic and GABAergic receptor scaffolding proteins, PSD-95 and Gephyrin respectively, interact to regulate the number of excitatory and inhibitory synapses thereby affecting the physiological E/I balance. To test if the effects of fluoxetine and MD were global or localized to the primary visual cortex (V1), we compared the frontal cortex, somatosensory cortex, and V1, contralateral and ipsilateral to the deprived eye. We found that MD caused an overall loss of synaptic proteins and a shift in favor of PSD-95. Surprisingly, fluoxetine alone had no impact on protein expression, but when it was combined with MD it prevented the MD-induced changes. Furthermore we found that these effects were restricted to the contralateral V1. Our results support two conclusions. First, MD causes a homeostatic shift towards greater excitation in the cortical area that lost the greatest amount of neural activity. Second, despite reported changes in gene expression, fluoxetine alone does not change protein expression. Rather, fluoxetine's latent effects are only revealed when it is combined with a strong manipulation of neural activity.

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Poster

599. Striate Cortex Plasticity

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Topic: D.04. Vision

Support: NIH Grant AA022455

NIH Grant AA13023

Title: Role of creb on the regulation of ocular dominance plasticity

Authors: ***N. S. PULIMOOD**, A. E. MEDINA;
Pediatrics, Univ. of Maryland Baltimore, Baltimore, MD

Abstract: The transcription factor CREB (cAMP Response Element Binding factor) plays a critical role in neuronal plasticity. In previous years, CREB has been implicated in both LTD and LTP, synaptic phenomena that are crucial for the depression and potentiation components of ocular dominance plasticity (dc-ODP and pc-ODP respectively). However the role of CREB in these *in vivo* processes is poorly known. Here we investigated the role of CREB in pc-ODP and dc-ODP, either by blocking or overexpressing CREB *in vivo* in the visual cortex during a critical period of development. We infected mice with a Herpes Simplex viral vector expressing either a dominant negative form or constitutively active form of CREB (CREB-DN or CREB-CA respectively), and chronically implanted electrodes in the binocular zone of the visual cortex. We then recorded visually evoked potentials in awake animals before and after 5 days of monocular deprivation (MD). This 5 day period allows us to distinguish the contributions of dc-ODP and pc-ODP to visual cortex plasticity. In a naïve animal, there is a temporal aspect to the manifestation of ODP - visual cortical responses to stimulation of the deprived eye depress (dc-ODP) after 3 days of MD, but cortical responses to stimulation of the open eye potentiate (pc-ODP) only after 5 days of MD. In CREB-DN infected animals, after 5-7 days of MD, we find that dc-ODP remains intact, but pc-ODP is disrupted. Moreover, CREB-CA infected mice present pc-ODP after only 2 days of MD. These results show that CREB is required for pc-ODP to occur and that overexpression of CREB may induce pc-ODP early, which together support a critical role of CREB in the temporal manifestation of ocular dominance plasticity.

Disclosures: **N.S. Pulimood:** None. **A.E. Medina:** None.

Poster

599. Striate Cortex Plasticity

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Topic: D.04. Vision

Support: R00NS076364

Title: Arc gates the expression of critical period ocular dominance plasticity in the visual cortex

Authors: *K. R. JENKS[1], E. PASTUZYN[2], J. ICHIDA[1], H. BITO[3], M. BEAR[4], J. SHEPHERD[1];
[2]Neurobio. and Anat., [1]Univ. of Utah, Salt Lake City, UT; [3]Univ. of Tokyo, Tokyo, Japan; [4]MASSACHUSETTS INSTITUTE OF TECHNOLOGY, Cambridge, MA

Abstract: Critical periods in development allow rapid acquisition of new skills and refinement of neuronal circuits involved in sensory processing. Ocular dominance (OD) plasticity in the visual cortex (VC) is well characterized and a useful tool to study the molecular mechanisms that underlie critical periods. In juvenile animals, brief closure of one eye results in a decrease of input from the closed eye and an increase of input from the open eye. In adult animals, this OD plasticity is absent. Expression of the immediate early gene *Arc* is required for many forms of synaptic plasticity, and mice lacking *Arc* exhibit deficits in OD plasticity. Thus, we hypothesize that *Arc* is a permissive factor that gates the critical period of OD plasticity. Moreover, we predict that expression of Arc declines with age, and that this decrease contributes to the loss of OD plasticity in adult animals. To test this hypothesis we examined OD plasticity in transgenic mice overexpressing Arc under an activity-dependent promoter. Visually evoked potentials were recorded in layer 4 of the VC prior to and following monocular deprivation at 1, 3, 6 and 9-month timepoints. Preliminary data show that Arc transgenic mice maintained robust OD plasticity even at 9 months of age, while little plasticity was apparent in wild-type littermate controls. To test if the loss of plasticity in wild type mice correlated with a decrease in Arc expression in VC, we used immunohistochemistry and Western blotting to quantify levels of Arc protein in mice at 1, 3, 6, 9 and 12-month time points. Our data indicates that in wild-type mice, Arc expression peaks at 1 month of age, corresponding to the peak of the critical period. However, Arc levels decreased drastically around 3 month of age, and there was little if any expression in mice at 9 and 12 months. In contrast, the transgenic mice maintained significantly higher levels of Arc at all ages. We will test the sufficiency of Arc in controlling OD plasticity by acutely injecting lentivirus containing the Arc open reading frame and promoter into wild-type adult mouse VC. Our results suggest that decreased expression of important synaptic

plasticity genes in excitatory neurons, perhaps via increased inhibitory network activity, leads to a reduced capacity for plasticity in adult brains. Arc may, therefore, be a novel target to enhance adult plasticity and cognition.

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Poster

599. Striate Cortex Plasticity

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Support: ERC-2009-AdG249425 – CriticalBrainChanges

Title: Increased visual cortical thickness in sight-recovery individuals

Authors: *M. J. GUERREIRO, M. V. ERFORT, J. HENSSLER, L. PUTZAR, B. ROEDER; Univ. of Hamburg, Hamburg, Germany

Abstract: Studies in permanently blind individuals have started to shed light onto the consequences of visual deprivation on brain morphology. These studies have shown that congenital or early blindness is associated with increased cortical thickness in a number of occipital brain areas, including the calcarine sulcus, cuneus, lingual gyrus and lateral occipital cortex. In contrast, whether cortical thinning observed in typical brain development is linked to a sensitive phase is not yet known. In the present study, we assessed cortical thickness of occipital brain areas in a group of six cataract-reversal individuals (aged 23-45 years, M = 32.7, SD = 8.5, 3 females) and in a group of six age- and gender-matched normally sighted controls (aged 18-45, M = 31.8, SD = 10.0, 4 females). The results revealed that cataract-reversal individuals exhibited higher cortical thickness than normally sighted controls in the left calcarine sulcus and bilaterally in the superior occipital gyrus and transverse occipital sulcus. Furthermore, occipital cortical thickness in cataract-reversal individuals correlated negatively with behavioral performance in an audio-visual task for which visual input was critical (Putzar et al., 2007), suggesting that the higher the visual cortical thickness, the lower the behavioral performance of cataract-reversal individuals. The present results demonstrate that early sensory experience plays a crucial role in shaping brain structure and suggest that the lack of experience-guided synaptic pruning during a sensitive phase of brain development might be maladaptive in cases of sight restoration.

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Poster

599. Striate Cortex Plasticity

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Topic: D.04. Vision

Support: NIMH Silvio Conte Center 1P50MH094271

Nakajima Foundation

Title: Transient loss of cross-modal influence in primary visual cortex by experience and inhibition

Authors: *R. HATTORI[1,2], T. K. HENSCH[1,2];
[1]Mol. and Cell. Biol., Harvard Univ., Cambridge, MA; [2]Neurol., Boston Children's Hosp., Boston, MA

Abstract: Early blind or deaf subjects dramatically rewire their brains to accommodate remaining modalities in visual or auditory brain regions, respectively. How this occurs and to what extent primary sensory areas may process other input remains largely unknown. Using intrinsic flavoprotein imaging and electro-physiological recordings from mice, we show that even primary visual (V1) cortex is weakly multimodal throughout life and that this cross-modal influence shifts dynamically during a critical period in postnatal development. Sound alone is able to evoke weak auditory signals in V1 and the cross-modal audiovisual interactions follow an inverse effectiveness rule (weaker visual responses are preferentially boosted), as in other classically-defined multisensory areas. This in turn impairs orientation and direction selectivity of the visual response. Interestingly, cross-modal auditory input to V1 is developmentally regulated, becoming tightly excluded specifically during a critical period for visual development. Maturation of inhibitory circuits within V1 is known to open this critical period. Using dark-exposure, GAD65 knockout mice or benzodiazepine pharmacology, we found that visual experience or the level of GABA function reversibly masked the cross-modal auditory response. Our results demonstrate that mouse V1 is essentially multimodal and has a mechanism to limit the impact of non-visual inputs during a key moment of developmental plasticity. Tight exclusion of cross-modal noise during the critical period increases signal-to-noise ratio for the primary visual modality and may promote the functional maturation of V1 as “visual” cortex.

Disclosures: **R. Hattori:** None. **T.K. Hensch:** None.

Poster

599. Striate Cortex Plasticity

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Topic: D.04. Vision

Support: NIMH T32 Training Grant: T32MH096678

Title: Nicotinic modulation of somatostatin interneurons reactivates plasticity in adult visual cortex

Authors: ***M. SADAHIRO**[1,2], M. DEMARS[1,2], P. BURMAN[1,2], H. MORISHITA[1,2,3,4,5];
[2]Psychiatry, [3]Friedman Brain Inst., [4]Opthalmology, [5]Mindich Child Hlth. and Develop. Inst., [1]Icahn Sch. of Med. At Mount Sinai, New York, NY

Abstract: A network of cortical inhibition is critical for experience-dependent plasticity in the visual cortex (V1). Although the role of Parvalbumin (PV)-interneurons on plasticity has been extensively studied, contributions of other GABAergic neurons such as those expressing somatostatin (SST) had largely been largely unexplored. Here we aimed to identify the novel molecular and circuit mechanisms governing the regulation of plasticity through SST-interneurons. Enriched in SST-interneurons, Lypd6 is a positive nicotinic modulator belonging to the same family as Lynx1, a known nicotinic plasticity brake expressed in PV-interneurons. Lypd6 expression in V1 decreased after critical period for ocular dominance plasticity in concert with declining plasticity across development. Transgenic neuronal overexpression of Lypd6 led to prolonged plasticity in the adult V1. Viral overexpression specifically in adult SST-interneurons, but not in pyramidal neurons, reactivated V1 plasticity. This effect required the α2 nicotinic acetylcholine receptor, which is highly enriched in Lypd6-positive SST-interneurons. The Lypd6-based plasticity was normalized by chemogenetic activation of PV-interneurons, highlighting a key role of SST→PV disynaptic inhibitory circuits. These results identify the first molecular and circuit mechanisms of V1 plasticity regulation by SST-interneurons and provide novel therapeutic targets for enhancing brain plasticity as means of functional recovery from neurodevelopmental disorders such as amblyopia. *MS, MD Equal Contribution

Disclosures: **M. Sadahiro:** None. **M. Demars:** None. **P. Burman:** None. **H. Morishita:** None.

Poster

600. Motion Processing

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Topic: D.04. Vision

Support: NEI Intramural Research Program

Title: Enhancement and suppression of motion signals by static stimuli in the human visual system

Authors: *C. QUAIA, B. M. SHELIGA, L. M. OPTICAN, B. G. CUMMING;
LSR, Natl. Eye Inst., Bethesda, MD

Abstract: Perhaps because static stimuli cannot produce a directional signal, their impact on motion processing has rarely been studied. This leaves open the possibility that static stimuli might significantly influence the processing of motion signals. To address this question we measured reflexive ocular following responses (OFRs) in three human subjects presented with a large (28 deg diameter) drifting 1D grating (either sinusoidal luminance modulation or band-passed white noise) to which we added a static mask (a 1D grating of the same kind). We found that the strength and sign of the interaction varied as a function of the relative orientation and contrast of the two gratings. A parallel static mask had a powerful suppressive effect. By varying independently the contrast of the two gratings, we found that the effect appears divisive: if the relationship between the magnitude of the OFR and the contrast of the moving grating is fitted with a Naka-Rushton function, increasing the contrast of the mask simply increases the semi-saturation constant. When the contrast of the two gratings was fixed, the strength of suppression varied as a function of the spatial frequency of the two gratings, but not simply as a function of their relative frequency. In contrast, the addition of an orthogonal static mask could either suppress or enhance the response to a moving grating. Enhancement was observed when the contrast of the static mask was lower or equal to that of the moving grating; suppression was observed otherwise. Enhancement was only observed when the orthogonal static mask and the moving stimulus were presented to the same eye. Suppression with a parallel mask was instead observed in both uniocular and dichoptic conditions, although stronger in the uniocular case. With noise stimuli we were also able to test the effect of changing the temporal structure of the mask (without adding a directional signal). We found that suppression was strongest when the parallel mask was static, intermediate when it was generated anew in each frame (uncorrelated), and relatively weak when it was present for a single frame (5 ms). In contrast, enhancement was equally strong when the orthogonal mask was static, uncorrelated across frames, or presented for two successive frames only, and still sizeable when presented for a single frame. We thus found

(at least) two mechanisms at work. One is suppressive, binocular, stronger for parallel orientations and prefers static stimuli. The other is facilitatory, monocular, stronger for orthogonal orientations, and insensitive to temporal structure.

Disclosures: C. Quaia: None. **B.M. Sheliga:** None. **L.M. Optican:** None. **B.G. Cumming:** None.

Poster

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German research foundation grant Nr EXC307

Max Planck Society Germany

Title: Optic flow links BOLD suppressed early visual cortex to areas encoding heading direction as predicted by predictive coding

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Abstract: Along the visual processing stream, information is conveyed in a feed-forward manner, from the analysis of simple visual features, to stages that process complex concepts. However, superimposed on this feed-forward pathway, feedback connections convey higher-level information to cortical areas lower in the hierarchy. A prominent framework for these connections is the theory of predictive coding [1] where high-level areas send stimulus interpretations to areas upstream in the hierarchy, which in turn resend prediction errors. Along these lines a growing body of neuroimaging studies show that predictable stimuli evoke smaller blood oxygen level dependent (BOLD) responses than otherwise matched non-predictable counterparts. The origin of such modulatory feedback signals is however widely unknown. Using functional magnetic resonance imaging (fMRI) in healthy human observers we here re-examine the robust finding of relative BOLD suppression that arises when a visual optic flow stimulus is contrasted to a random motion stimulus with matched low-level features [2, 3]. Using functional connectivity analysis we show a highly specific link between BOLD suppressed early visual cortex and two areas known to encode heading direction: entorhinal cortex (EC) and an area in

precuneus (PreC), bordering retrosplenial cortex (RSC). Our results provide first evidence that BOLD suppression for predictable stimuli are indeed mediated by specific high-level areas as predicted by the theory of predictive coding. **References** 1. Clark, A. (2013). Whatever next? Predictive brains, situated agents, and the future of cognitive science. Behav Brain Sci *36*, 181-204. 2. Braddick, O.J., O'Brien, J.M., Wattam-Bell, J., Atkinson, J., Hartley, T., and Turner, R. (2001). Brain areas sensitive to coherent visual motion. Perception *30*, 61-72. 3. McKeefry, D.J., Watson, J.D., Frackowiak, R.S., Fong, K., and Zeki, S. (1997). The activity in human areas V1/V2, V3, and V5 during the perception of coherent and incoherent motion. Neuroimage *5*, 1-12.

Disclosures: **A. Schindler:** None. **A. Bartels:** None.

Poster

600. Motion Processing

Location: Hall A

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Program#/Poster#: 600.03/L7

Topic: D.04. Vision

Title: Spike-field coupling of the anterior cingulate cortex and frontal eye field in goal-directed eye movements

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[1]Neurosci., Western Univ., London, ON, Canada; [2]Yale Univ., New Haven, CT; [3]York Univ., Toronto, ON, Canada

Abstract: Although numerous functional imaging studies in human subjects have shown that the frontal eye fields (FEF) and anterior cingulate cortex (ACC) are co-activated during cognitively demanding saccade tasks, single unit and local field potential (LFP) studies in nonhuman primates have shown important differences in the activity between these two areas. Little is known about the coupling of spiking activity and local field potentials in these areas. Here we investigated the spike-field synchrony of ACC and FEF neurons with the corresponding LFPs recorded at the same area while monkeys performed a memory-guided saccade task and a pro/anti-saccade task. During the delay period of the memory-guided saccade task, ACC units exhibited increased low gamma (30-60Hz) coupling prior to ipsiversive saccades whereas FEF units displayed increased high gamma (60-100Hz) synchrony prior to contraversive saccades. This finding supports the saccade-generating role of the FEF for contraversive saccades and suggests a potential inhibitory role of the ACC. Furthermore, ACC and FEF units showed a

different pattern of coupling during the preparatory period of the pro/anti-saccade task. ACC units exhibited an increased theta band (3-8Hz) coupling in pro- vs. anti-saccade trials and no difference across gamma band coupling. Similar to the ACC units, FEF units exhibited increased coupling to the theta band for pro-saccades and an increased gamma band (60-100Hz) coupling of FEF units for anti-saccades compared to pro-saccades. These findings support a role of the theta band in rule maintenance, whereas the gamma band may be more involved in motor-related functions. Taken together, our results indicate that theta and gamma oscillations have different roles in cognitive processes and these frequency bands are modulated differently across ACC and FEF.

Disclosures: **S. Babapoor-Farrokhran:** None. **M. Vinck:** None. **T. Womelsdorf:** None. **S. Everling:** None.

Poster

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Program#/Poster#: 600.04/L8

Topic: D.04. Vision

Support: ONR N00014-14-1-0359

Title: How does the visual system recover object motion during self-motion?

Authors: *O. W. LAYTON, B. R. FAJEN;
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Abstract: To move effectively through dynamic environments, humans must perceive both the direction of self-motion and the trajectories of moving objects. While humans perceive the movement of objects relative to a stationary world (world reference frame), optic flow reflects the motion of objects and the background relative to the moving observer (observer reference frame), not the world. The visual system must not only determine what flow is attributed to self- and object motion, but recover object motion in a world reference frame. The importance of this problem has inspired research on the visual conditions in which object motion is recovered, but the underlying mechanisms in the visual system remain unclear. We present a simple model of primate visual areas MT and MSTd that explains how the visual system dynamically estimates both self-motion and object motion in a world reference frame. The optic flow field, which may consist of motion due to the observer and/or moving objects, activates MT cells tuned to different motion directions. Model MSTd responds to the radial, spiral, or translational pattern

most similar to the global flow and estimates the self-motion direction (Duffy & Wurtz, 1991; Layton & Browning, 2014). The model proposes that MT and MSTd recover object motion in a world reference frame through two interacting processes. First, to enhance the self-motion direction estimate, MSTd cells send feedback to inhibit MT cells that do not signal a motion direction that is consistent with the global flow pattern. This changes the population-coded motion direction of cells responding to the discrepant object motion. Second, model MT neurons tuned to opposing motion directions locally compete with one another (Albright et al., 1984; Heeger et al., 1999). An object passing over a discrepant flow pattern deactivates MT cells responding to the background flow and generates rebound activity in cells tuned to the opponent motion direction through disinhibition. The feedback from MSTd and opponent competition in MT shift the population-coded motion direction of the object toward that in a world reference frame. Model simulations show that object motion estimates are similarly affected as human visual judgments under a range of conditions (Warren & Rushton, 2008; 2009). A number of predictions emerge from our model, including that heading need not be estimated for the trajectory of an object to be recovered in a world reference frame. Our model is compatible with the flow parsing hypothesis (Warren & Rushton, 2005), but proposes specific physiological mechanisms and clarifies how self-motion and object motion estimates interact.

Disclosures: **O.W. Layton:** None. **B.R. Fajen:** None.

Poster

600. Motion Processing

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Topic: D.04. Vision

Support: Supported by the NIMH IRP

Title: Comparing the specification of facial motion in macaques and humans

Authors: *H. ZHANG[1], A. STACY[2], S. JAPEE[2], L. UNGERLEIDER[2];
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Abstract: Dynamic faces convey a wealth of social information. Both macaques and humans depend on facial motion to facilitate the recognition of facial expression in their social interactions. However, the extent to which the specialization for facial motion is represented in the visual systems across the two species remains unclear. Here, we used fMRI to investigate this issue. Four male macaque monkeys were injected with MION prior to fMRI scanning at 4.7T.

During scanning, they viewed blocks of the following four stimulus categories: dynamic frontal-view neutral monkey faces, dynamic common objects, static frontal-view neutral monkey faces, and static common objects. Twenty human subjects participated in a similar fMRI experiment at 7T, in which they viewed blocks of the identical four stimulus categories, except they viewed human faces. For both monkeys and humans, the static face/object stimuli were extracted from the corresponding dynamic video stimuli, and the motion energy in the dynamic face blocks was equated to that in the dynamic object blocks, using an optic flow algorithm. To localize the face-selective regions in the two species, both monkeys and humans also performed separate localizer runs, in which we contrasted activations evoked by images of static faces and static objects. General linear model analyses were performed on whole brain fMRI data to evaluate the fMRI responses evoked by the four stimulus categories. The contrast of the fMRI response to motion caused by faces (dynamic faces versus static faces) relative to the fMRI responses to motion caused by objects (dynamic objects versus static objects) was used to define the location of the brain areas selective for facial motion. Our results showed that, in all four monkeys, significant activations evoked by facial motion were found in the anterior superior temporal sulcus (STS), within the anterior fundus face patch bilaterally ($p<0.001$). In humans, facial motion activated three separate foci in the right STS ($p<0.001$): anterior STS, middle STS and posterior STS, with the anterior STS focus showing the most significant selectivity for facial motion. Taken together, our results suggest that monkeys and humans share similar neural substrates within the anterior STS for the processing of facial motion.

Disclosures: **H. Zhang:** None. **A. Stacy:** None. **S. Japee:** None. **L. Ungerleider:** None.

Poster

600. Motion Processing

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Program#/Poster#: 600.06/L10

Topic: D.04. Vision

Support: Mitacs

Title: A large-scale phenomenological model of activity in primate area mt

Authors: *O. SADAT REZAI, B. TRIPP;
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Abstract: One of the major barriers to modelling the primate visual cortex is the complexity of the network. Since each visual area receives input from many other areas, modelling any

subnetwork without ignoring most of its inputs is difficult. One possible way to mitigate this problem is to develop phenomenological (stand-alone) models of various visual areas, which produce realistic spike patterns, and then use them as inputs to more physiologically detailed models of other areas. We are developing such a phenomenological model of primate area MT and hope to use it, as input to mechanistic models of the other areas to which MT projects (e.g. V1, V2, V4, TEO). We developed the model structure and estimated distributions of its parameters using data from the electrophysiology literature. Each physical location in MT is associated with a probability density function over the model parameters. Our model consists of topographically organized units with lateral interactions [1], which are driven by linear kernels that combine input from several fields. The fields include motion, binocular disparity, contrast, and attention. Some of these (e.g. contrast) can be computed fairly directly from video input. Others (e.g. motion and disparity) are estimated using more sophisticated methods from computer vision. Finally, the attention field is manually defined in each frame of the input videos. These methods produce time-varying spike rates, which we convert to spike trains using a Poisson model with correlations. Our approach is data-driven, in that we simply try to produce statistically realistic spike trains without making any assumptions about mechanisms. On the other hand, it is necessary to extrapolate beyond published data in order for the whole MT model population to respond to a variety of stimuli. 1. Rubin, D. B., Van Hooser, S. D., & Miller, K. D. (2015). Neuron, 85(2), 402-417. 2. Treue, S., & Trujillo, J. C. M. (1999). Nature, 399(6736), 575-579. 3. Pack, C. C., Hunter, J. N., & Born, R. T. (2005). Journal of Neurophysiology, 93(3), 1809-1815. 4. Pack, C. C., & Born, R. T. (2001). Nature, 409(6823), 1040-2.

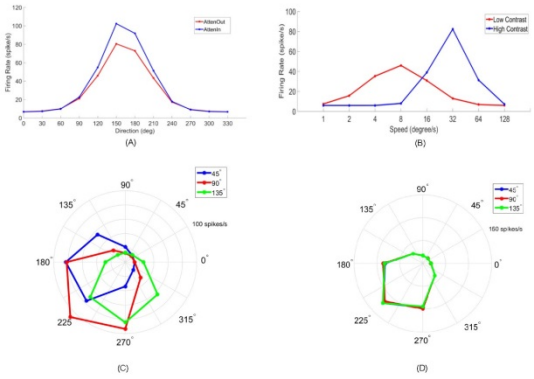

Figure: Illustration of the model's fits to a variety of tuning curves from the electrophysiology literature: (A) Effect of directing attention inside (blue curve) versus outside (red curve) the receptive field on the directional tuning curve (compare to Figure 1.B in [2]). (B) Speed-tuning of an MT neuron at low (red curve) and high (blue curve) contrasts (compare to Figure 1.C in [3]). (C, D) Evolution of direction tuning for three oriented moving bars (i.e. 45°, 90°, and 135° angle-difference between the major axis of the moving bar and the direction of motion in blue, red, and green respectively). Direction tuning is represented in polar coordinates. (C) Earliest direction-tuned response for a single MT neuron. (D) Direction tuning for the same MT cell averaged over the last 1,500ms of the stimulus presentation (compare to Figure 2.A,B in [4]). All the results shown in this figure belong to the simulations where we drove our model with laboratory stimuli (e.g. moving bars and random dots) so that we could fit our model to existing tuning curves in the literature. However, we also used natural stereo videos from the computer vision community (i.e. KITTI Dataset) to drive our model.

Disclosures: **O. Sadat Rezai:** None. **B. Tripp:** None.

Poster

600. Motion Processing

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Topic: D.04. Vision

Support: EY7977

EY9314

Title: Interactions of local motion signals

Authors: ***E. I. NITZANY**[1,2], M. LOE[3], S. E. PALMER[3,4], J. D. VICTOR[2];
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Abstract: Motion signals are underlie basic visual tasks, such as figure/ground segregation and navigation. Visual motion analysis is considered to consist of two stages: extraction of local motion cues, followed by integration of these cues across space. Three kinds of local motion signals can be distinguished, based on the kinds of spatiotemporal correlations that generate them: Fourier (F), based on 2-point correlations (Reichardt 1961); non-Fourier (NF), based on 4-point correlations (Chubb & Sperling 1988); and glider (G), based on 3-point correlations (Hu & Victor 2010). G signals have two sub-types, expansion and contraction, associated with objects that are looming and receding, respectively. Detection of isolated G and NF signals cannot be mediated by a purely multiplicative cross-correlator or a purely quadratic motion energy model. G signals have recently attracted substantial attention, following the demonstration that a wide range of species (human, macaque, zebrafish, dragonfly, and fruitfly) respond to them in similar ways - suggesting that there are advantages to using these signals in visual tasks. In natural scenes, F and G signals tend to occur together (Nitzany & Victor, 2014), and this puts a focus on how these motion cues interact. Here, we study this with synthetic movies that contain controlled levels of each kind of signal but are otherwise as random as possible, as formalized by a maximum-entropy criterion. Subjects were asked to report the perceived motion direction in a 2-alternative forced choice task, following viewing of 1-sec clips of these movies (20x30 grids of 0.45 x 0.45 deg checks, 10 frames/sec). Thresholds were determined via standard Weibull-function fits. In separate experiments, two cue combinations (F with G contraction, or F with G

expansion) were studied; within each experiment, various levels of F and G signals were randomly interleaved. For combinations of F with G contraction (N=4), we found that subthreshold cues combine, and the combination is approximately quadratic. In addition, there was a suggestion of light vs. dark asymmetry: F signals interacted more strongly with G contraction signals carried by light regions than with G contraction signals carried by dark regions. Interestingly, for combinations of F with G expansion (N=3, including two studied with G contraction), we observed a different kind of interaction: the sensitivity to F signals was reduced in the context of trials that included G expansion signals. In summary, we report that local motion signals of different types interact at the perceptual level, and that this interaction can include subthreshold summation and context-dependent changes in sensitivity.

Disclosures: **E.I. Nitzany:** None. **M. Loe:** None. **S.E. Palmer:** None. **J.D. Victor:** None.

Poster

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Max Planck Society Germany

Title: Speed encoding in human motion regions for objective and retinal motion

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Abstract: The visual system continuously updates visual perception in order to compensate for eye-, head- or body- movements in order to create a stable perception of the world surrounding us. This mechanism is needed not only for a stable and coherent perception, but also for distinguishing objective (‘real’) motion induced by moving objects from that induced by eye movements. Previously, human visual areas V3A and V6 have been shown to compensate for self-induced retinal motion and to encode objective motion during smooth pursuit eye movements (Fischer et al., 2012). However, it is unclear how responses to objective and retinal motion vary as a function of speed in these and other human motion responsive regions. Prior studies examining fMRI responses as a function of speed always measured joint responses to

objective and retinal motion, as speed of the background motion was varied during fixation (Chawla et al., 1998). In this study we used a pursuit paradigm that allowed us to measure responses to objective and retinal motion separately (Fischer et al. 2012). We did this for 6 different levels of speed (1, 2, 4, 8, 16, and 24 degrees per second) in order to obtain speed tuning profiles for separately localized visual motion regions. Stimuli consisted of moving fourier scrambles derived from natural images. We found that all regions had either a trend or significant response increase with higher speeds for both, retinal and objective motion. V3A stood out in that it was the only region in which speed increases in objective motion lead to a higher signal modulation than speed increases in retinal motion. In other words, the slope related to speed increase was significantly higher for objective than for retinal motion only in V3A. In addition, V3A had significantly higher responses to objective than to retinal motion at all speeds. V6 responses resembled those to V3A, but were less pronounced. V5/MT and MST did not differ in objective and retinal speed slopes, even though both tended to respond more to objective motion at all speeds. These results support the view that human V3A (and V6) play a predominant role in integrating visual signals with efference copies, and that it encodes primarily objective rather than retinal motion signals. Chawla, D., Phillips, J., Buechel, C., Edwards, R., Friston, K.J., 1998. Speed-dependent motion-sensitive responses in V5: an fMRI study. Neuroimage 7, 86-96. Fischer, E., Buelthoff, H.H., Logothetis, N.K., Bartels, A., 2012. Human areas V3A and V6 compensate for self-induced planar visual motion. Neuron 73, 1228-1240.

Disclosures: D. Korkmaz Hacialihafiz: None. **G. Darmani:** None. **A. Bartels:** None.

Poster

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Title: Neural activity in occipito-parietal and frontal regions predicts outcome of bistable motion perception

Authors: *Q. CHEN[1], L. SHEN[2], B. HAN[3,4], J. XIA[2], L. CHEN[5];
[1]South China Normal Univ., Guangdong, China; [2]South China Normal Univ., Guangzhou, China; [3]Univ. de Toulouse, Ctr. de Recherche Cerveau et Cognition, Univ. Paul Sabatier, Toulouse, France; [4]Ctr. Natl. de la Recherche Scientifique, Unité Mixte de Recherche 5549, Faculté de Médecine de Purpan, Toulouse Cedex, France; [5]Dept. of Psychology, Peking Univ., Beijing, China

Abstract: Upon viewing dynamic ambiguous visual stimuli, observers often experience spontaneous transitions between two competing percepts although the physical stimulation remains unchanged. This phenomenon is termed as “bistable perception”. It remains unknown the neural causes that generates one specific perception during the bistable phenomenon. By applying fMRI and EEG to record brain activity during the presentation of bistable apparent motion stimuli, we asked participants to report whether the element or group motion they perceived and tested how trial-to-trial variation in pre-stimulus activity predicted element motion or group motion during the bistable perception. Element motion perception arised with enhanced pre-stimulus activity in the parietal and prefrontal cortex and reduced pre-stimulus activity in the default-mode-network, and manifested as increased connectivity between the parietal cortex and the premotor regions upon the appearance of the bistable stimuli. Moreover, reduced alpha/theta power within 400 ms before the stimulus predicts the perception of the element motion. The activation of the parieto-frontal attentional network and reduced alpha power implicated the element motion perception was modulated by attention even before the stimulus appeared. Furthermore, the phase of alpha (7-16Hz) oscillations within 200 ms before the stimulus significantly covaried with the perceptual outcome: if the alpha oscillation reached a certain phase (strong phase-locking value), the group motion percept occurred; if not (weak phase-locking value), the element motion perception occurred. This effect was observed in occipito-parietal regions, as well as in a distant frontocentral region. But the effect appeared earlier in the occipito-parietal regions (~170ms before the stimuli) than in the frontocentral regions (~130ms before the stimuli), indicating the oscillation of the two regions contributed differentially to the bistable motion perception. Therefore, our results suggest the different characters of the neural activity can predict specific motion perception during the bistable apparent motion.

Disclosures: **Q. Chen:** None. **L. Shen:** None. **B. Han:** None. **J. Xia:** None. **L. Chen:** None.

Poster

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Title: Prediction error signals for visuo-motor mismatch in human visual cortex

Authors: *J. HEINZLE[1], K. STEPHAN[1,2,3], G. B. KELLER[4];
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Abstract: Our own movements change our visual input. In order to detect "true" changes of the environment, the nervous system needs to account for self-generated changes of sensory input. Here, we investigated how a visuo-motor mismatch drives prediction error (PE) signals in the human brain using a paradigm that allowed us to distinguish between purely visual mismatch and mismatch related to how motor actions (moving a joystick with the hand) changed visual sensations. We obtained fMRI data from 31 healthy adult volunteers controlling the movement of an expanding/contracting random dot pattern with a joystick. In 20% of the trials, a visuo-motor mismatch was introduced by inverting the direction of dot movement. In additional runs, participants passively viewed exactly the same visual stimulation, including visual mismatches. After standard preprocessing, we used a general linear model with regressors for run types (active vs. passive), directions of movement (forward vs. back) and the conditions (match vs. mismatch). The main contrast of interest was the interaction between match vs. mismatch and active vs. passive. Statistical significance was assessed using family wise error cluster level correction for multiple comparisons across the whole brain ($p_{cluster} < 0.05$, voxel threshold $p < 0.001$) and permutation testing for regions of interest (ROI) analysis ($p<0.05$). Significant visuo-motor mismatch activity was observed predominantly in bilateral prefrontal and parietal areas. In addition, regions in the right anterior insula, the left inferior temporal gyrus and the right middle occipital gyrus showed whole brain corrected activations. The ROI analysis revealed significant visuo-motor mismatch in human MT, but not in primary visual cortex (V1) or motor cortex (M1). In conclusion, we demonstrate that in addition to strong activation of bilateral parietal and prefrontal areas visuo-motor mismatch leads to activation in early visual area MT. Importantly, these PE signals are driven by mismatch between one's own actions and the resulting visual input - not simply by visual mismatch. The whole brain results are in agreement with other PE studies in humans showing e.g. robust activation of prefrontal areas. In addition, similar to a recent mouse model of visuo-motor mismatch in the context of locomotion (Keller et al., Neuron, 2012), significant activation was observed in an early visual area - but not in V1. Future

studies are required to clarify whether this discrepancy is the result of species differences or related to differences in the paradigm (joystick movements vs. locomotion).

Disclosures: **J. Heinzle:** None. **K. Stephan:** None. **G.B. Keller:** None.

Poster

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Topic: D.04. Vision

Support: Max Planck Gesellschaft (MPG)

German Federal Ministry of Education and Research (BMBF), Germany, Grant FKZ: 01GQ1002

Title: Neural signals of motion integration are modulated by perception

Authors: ***Q. LI**[1,2], N. K. LOGOTHETIS[1,2,3], G. A. KELIRIS[1,2,4];
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Abstract: A very important feature of primate vision is the ability to integrate motion signals into a coherent percept. To this end, a two-stage motion integration model has been proposed that selectively integrates local signals over time and space to reconstruct the global motion pattern. It has been suggested that the first stage responsible for local motion detection takes place in lower level visual area(s), while a second stage in higher area(s) integrates the local motion signals in order to extract the global motion direction. Support for this hypothesis stems mainly from recordings in anesthetized non-human primates while evidence in awake-behaving ones is very limited. Furthermore, very little is known about how motion integration is influenced by perception. In this study, we designed a novel pseudo-plaid stimulus that can parametrically modulate coherent or transparent motion perception by changing local feature information. The stimulus consists of two types of apertures over a line plaid display. The first group of apertures allows only single contours to pass through while the second only intersections. Human psychophysics demonstrated that the motion perception changes parametrically with the proportion of the two types of apertures from 100% transparent when only single-contour apertures are present to 100% coherent when only intersection apertures are

displayed. Then, we used this stimulus and performed multi-electrode recordings in areas V1 and MT of alert macaques. Analysis of the firing rates during the whole trial (1000 ms) demonstrated that MT neurons were strongly modulated by the proportion of different aperture types reflecting the perception. Specifically, MT neural responses increased when motion perception was more coherent. In contrast V1 neurons did not show any significant changes by using this measure. These data corroborate the hierarchical organization of motion integration and demonstrate the relationship of neural signals with subjective perception.

Disclosures: Q. Li: None. **N.K. Logothetis:** None. **G.A. Keliris:** None.

Poster

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Topic: D.04. Vision

Support: NIH NEI EY023371

Title: Spatial integration of visual motion signals for smooth pursuit eye movements in humans and non-human primates

Authors: *C. SIMONCINI, T. MUKHERJEE, L. C. OSBORNE;
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Abstract: Humans and monkeys use smooth pursuit eye movements to track moving objects of interest. To determine the appropriate eye movement, the brain must integrate motion signals across the region of interest within the visual field. In order to understand the spatial and temporal extent of motion integration for pursuit, we have analyzed eye movements to motion noise stimuli. We created random dot kinetograms with a constant direction and speed of movement, but we added to each dot a stochastic direction and/or speed at each time step. Dot directions were drawn from a uniform distribution with 1 degree spacing. Dot speeds were uniformly distributed in N-space where v = 2N. We measured the pursuit responses of human subjects with a Dual-Purkinje infrared eye tracker and non-human primates using implanted scleral coils. We found that the spatial-temporal filter that minimized the squared error in predicted eye velocity and direction covered a circularly symmetric Gaussian amplitude profile. We found that the Gaussian filter had a SD of 5 degrees over a range of target manipulations (aperture size, dot density, aperture motion) for both humans and monkeys. The temporal

duration of the filter was 40 ms (FWHM) and was also constant across multiple target forms. The spatial temporal filter accounted for 61% of the variance (corr coeff2). If we differentially weighted sub-regions of the area of interest by local dot density and motion vector similarity, we could account for 80% of pursuit variance over time. The consistency of these findings across dot target forms with different levels of optic flow and species suggests that the integration window for pursuit may be largely constant.

Disclosures: C. Simoncini: None. **T. Mukherjee:** None. **L.C. Osborne:** None.

Poster

600. Motion Processing

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Topic: D.04. Vision

Support: FWO Grant 11Q7314N

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METH Grant /08/02

Title: EEG frequency tagging reveals neural integration in the perception of coordinated motion

Authors: *N. ALP[1], N. KOGO[2], B. ROSSION[3], J. WAGEMANS[2];
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Abstract: The point-light display (PLD) is one of the most frequently used stimuli to investigate the interaction between form and motion in biological motion perception. In a PLD, the motion of the individual dots, their specific configuration, and the spatiotemporal dynamics of their trajectories together give rise to the perception of a human figure carrying out a particular action. Here we combine multiple PLDs in one stimulus to investigate the mechanisms that are involved in processing coordinated movements and to identify the neural activity that is specific for the perception of globally coordinated movements. For this purpose, a frequency-tagging technique was applied in combination with the recording of EEG. In the experimental condition, the motions of the PLDs were coordinated as in a group of dancers. In two control conditions, the

coordinated motions and the perception of biologically plausible motion were diminished, respectively. Frequency tagging was implemented by modulating the luminance intensity of the point lights of the individual dancers with different frequencies for the different dancers (PLD1=f1 and PLD2=f2). Fast Fourier Transform was applied to investigate the effect of coordinated motion. It has recently been shown that neuronal populations that are involved in the integration of two differently-tagged stimulus parts can produce (non-linear) intermodulation (IM:f1±f2) components. Comparing IM effects between our coordinated motion condition and control conditions allows us to analyze the interaction and integration of the biological motions among the dancers, hence enabling us to identify the mechanisms and cortical areas that are involved in the perceptual integration of coordinated biological motion.

Disclosures: **N. Alp:** None. **N. Kogo:** None. **B. Rossion:** None. **J. Wagemans:** None.

Poster

600. Motion Processing

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Program#/Poster#: 600.14/L18

Topic: D.04. Vision

Title: A genome-wide association study of human visual motion perception

Authors: ***N. REN**[1,2], B. CHEN[2], Z. ZHU[2], Y. RAO[2], F. FANG[1];
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Abstract: Visual motion perception is an essential ability of human visual system. However, there are few genetic studies investigating the heritability of motion perception as a polygenetic cognitive trait. Here we employed a genome-wide association method to examine the genetics underlying visual motion perception. We measured the motion identification and motion discrimination abilities in a cognitively healthy cohort of Han population with normal vision. Visual stimuli were random dot kinematograms (RDKs) consisting of 400 dots moving at a velocity of 10°/s within a 8°-diameter circular area. In the motion identification task, participants were asked to indicate the perceived direction of coherent motion (1 of 8 possible directions: 0°, 45°, 90°, 135°, 180°, 225°, 270°, 315°) in a noisy RDK. We adopted a method of constant stimuli (MCS) to measure the motion coherence threshold for each subject, by changing the fraction of coherently moving dots in the RDK. For the motion discrimination, participants were instructed to discriminate between the motion directions of two successively presented RDKs (at 100% coherence) in a two-alternative forced choice (2AFC) task. We measured the direction

discrimination threshold for each participant, using the MCS. In both tasks, smaller thresholds indicated better performance. Since the behavioral performance showed substantial individual difference, we performed a genome-wide association study in 780 participants to identify motion-perception-related variants. Single nucleotide polymorphisms (SNPs) showing suggestive genomic significance were picked out for further validation study in a second cohort of 1468 Han people. The result showed that the SNP rs600416 linked with CSGALNACT1 (chondroitin sulfate N-acetylgalactosaminyltransferase 1) and rs2673467 related with KCNMA1 (potassium large conductance calcium-activated channel, subfamily M, alpha member 1) were significantly associated with motion identification and motion discrimination, respectively (both $p<0.05$). Evidence from these experiments suggests a possible role for these genes in human visual motion perception.

Disclosures: **N. Ren:** None. **B. Chen:** None. **Z. Zhu:** None. **Y. Rao:** None. **F. Fang:** None.

Poster

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Topic: D.04. Vision

Support: MRC

BBSRC

Title: Receptive field transformations between retinal ganglion cells and superficial inhibitory interneurons in zebrafish larvae

Authors: *F. ABBAS, M. P. MEYER;
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Abstract: Inhibition plays a crucial role in shaping sensory-evoked activity in the visual system, a better knowledge of inhibitory circuits is necessary for our understanding of how visual circuits operate. Here we use *in vivo* functional imaging to characterise the receptive field properties of superficial inhibitory interneurons (SINs) in the optic tectum of larval zebrafish. SINs are located in the most superficial part of the optic tectum, with arborisations that are laminar and within the superficial layers of the tectal neuropil. Recent studies have implicated these neurons as necessary in prey capture behaviour, as well as showing that these neurons exhibit size selectivity. Using a drifting grating stimulus we demonstrate the presence of three functional

subtypes of direction-selective (DS) SIN with preferred angles matching those of DS retinal ganglion cell inputs to tectum. Further we show that these exhibit bandpass spatial tuning, with preference for smaller gratings, matching the size of stimulus previously reported to elicit prey capture behaviour. Moreover we show that directional tuning bandwidth is significantly narrower than that seen in DS-RGCs- a feature that is insensitive to pharmacological blockade of GABA-A receptors suggesting an intrinsic mechanism that narrows directional tuning bandwidth. Our results show that SINs are highly selective for at least two visual features: size and direction of travel of visual objects. Whilst previous work on SINs has implicated them in a size selective circuit in the tectum, we propose that this may also involve directional selectivity.

Disclosures: F. Abbas: None. **M.P. Meyer:** None.

Poster

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Topic: D.04. Vision

Support: NIH MH065339

Title: Neural motion detection circuits underlying looming-evoked escape behaviors in *Drosophila*

Authors: *Y. KYUNG[1], H. DIERICK[2,1], F. GABBIANI[1,3];
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[3]Computat. and Applied Mathematics, Rice Univ., Houston, TX

Abstract: A recent study proposed that a class of neurons of the lobula/lobula plate, called Foma-1, is critical for the generation of escape jumps elicited by looming stimuli simulating the approach of an object on a collision course (de Vries and Clandinin, Curr Biol 22: 353-362, 2012). The local motion sensitivity of Foma-1 neurons suggests that they may receive directionally selective inputs. Recent electrophysiological evidence shows that T4 and T5 cells play an important role in the detection of directional motion in the context of optomotor behaviors (Mauss, et al., J Neurosci 34.6: 2254-2263, 2014). Several studies proposed that these neurons belong to two pathways originating with L1 and L2 that are specialized in detecting ON/OFF motion stimuli (Rister, et al., Neuron 56:155–170, 2007; Joesch, et al., J Neurosci 33:902–905, 2013; Behnia, et al., Nature 512.7515:427-430, 2014). The neuron L1 is presynaptic to Mi1 and Tm3 which both synapse onto T4, while L2 is presynaptic to Tm1 and Tm2 which

both synapse onto T5 (Stronther, et al., Curr Biol 24:976-983, 2014; Takemura, et al., Curr Biol 21: 2077-2084, 2011). Taken together, these studies suggest that these pathways provide input to Foma-1 neurons. We used a behavioral approach to investigate whether the ON and OFF pathways could provide inputs to Foma-1. To trigger escape jump, we used light (ON) and dark (OFF) looming stimuli presented on a dark and light background, respectively. We used the *GAL4/UAS* system to silence specific cell classes of neurons belonging to the two pathways. The transcription factor GAL4 was expressed specifically in lines targeting the following neurons: L1, L2, Mi1, Tm1, Tm2, Tm3, T4, T5, and Foma-1. GAL4 was used to drive expression of a temperature sensitive dominant negative mutation of *Drosophila* dynamin (*Shibire*) from a UAS promoter (Kitamoto, T, J Neurobiol 47.2:81-92,2001). When we presented ON stimuli at the restrictive temperature of approximately 30 °C, the jump probabilities of T4 blocked flies and L1 blocked flies were suppressed. The decrease in jump probabilities were similar to those observed in Foma-1 blocked flies. In contrast, the jump probabilities of T5 blocked flies and L2 blocked flies were decreased in response to OFF stimuli. Mi1 and Tm1 blocked flies also showed specific behavioral deficits to ON and OFF looming stimuli, respectively. These results show that T4, Mi1 and L1 mediate behavioral responses to ON looming stimuli, while T5, Tm1 and L2 mediate responses to OFF looming stimuli. Thus, our data provide evidence that the parallel pathways provide directional motion input to Foma-1 neurons. We are further investigating this hypothesis using imaging electrophysiology.

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Poster

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Title: FMRI brain activation in response to motion in school-age children born <33 weeks' gestational age who were supplemented with high-dose DHA - results from a follow-up of a randomized controlled trial

Authors: *C. S. MOLLOY[1], J. CHEN[2], R. BEARE[2,3], D. K. THOMPSON[2], S. STOKES[2,4], M. MAKRIDES[5,6,7,8], C. T. COLLINS[5,6,7,8], L. W. DOYLE[2,9,4], M. L. SEAL[2,4], P. J. ANDERSON[2,4];
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Abstract: Background: Children born preterm exhibit impaired motion processing. These deficits may be associated with inadequate supply of specific nutrients such as docosahexaenoic acid (DHA, 22:6 n-3) that affect the normal development of the eye and brain. Objective: The current study aimed to investigate the effects of DHA supplementation on motion processing performance and functional brain activation. Design: Follow-up of a subgroup of children from a multi-centre longitudinal randomized controlled trial. Infants were randomly assigned to milk containing a higher concentration of DHA (1% of total fatty acids, higher-DHA group) or a standard amount of DHA (0.2-0.3% total fatty acids as DHA, control group). The randomization schedule was stratified by sex and birth weight <1250 g or ≥1250 g. Functional magnetic resonance imaging scans were obtained during a global motion processing task for 48 (25 in the high-DHA group and 23 in the standard DHA group) children aged 7 years. Participants were also assessed on a high density and low density behavioral measure of global motion processing out of the scanner. Results: There were no behavioral differences in global motion processing between the high DHA and standard DHA groups, however both groups showed high rates of impairment. When attending to low-density dots moving coherently left or right the high DHA group exhibited a trend ($p=0.05$) toward decreased brain activation, primarily in the precuneus and cuneus, relative to the standard DHA group. Conclusions: Supplementing human milk with DHA at a dose of ~1% of total fatty acids given in the first months of life to very preterm infants appears to decrease functional activation relative to controls in the visually-related brain regions, precuneus and cuneus, but has no effect on performance.

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Poster

600. Motion Processing

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Support: DFG Research Fellowship

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Title: Visual motion processing during continuous naturalistic behaviors

Authors: *J. KNÖLL[1], J. W. PILLOW[2], A. C. HUK[3];
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Abstract: Everyday life requires dynamic matching of behavior to the tasks at hand. Depending on the task, very different parts of information in the visual field should be used. This is often studied with static attentional paradigms with a single discrete response for each trial. These tasks also typically require significant training. However, this does not match well to natural task-dependent behavior, where both the goal and the distribution of information can change continuously. Thus, very little is known about how the brain accomplishes task-dependent selection and integration of information in more naturalistic continuous behavior. We therefore developed a novel paradigm which allows quantification of the temporal and spatial visual parameters that drive behavior in a continuous ocular tracking task, and which is also suitable for characterizing motion-selective neurons. Here we report behavioral results from this paradigm. The core stimulus consisted of a moving cloud of dots creating a large field optic flow (80 x 50 deg of visual angle). The focus of expansion (FOE) of the flow field moved continuously according to a random walk. To characterize the spatial integration of the visual motion, we divided the field into hexagonal subfields. Each subfield either had a small, random perturbation from the motion associated with the “true” FOE or could be blank. Perturbations of the subfields

were resampled randomly every 33 to 1000 ms. Both macaques and humans intuitively tracked the FOE. To maintain interest and solidify FOE tracking, we dispensed reward periodically whenever gaze was within 7.5 deg of the FOE for a few seconds. Trials ended when gaze left the screen for more than 250 ms or after 300 s of visual stimulation (mean duration, macaque: 23 s, human: 245 s). We used regression to determine the spatiotemporal parameters that best predicted the subject's gaze. When 45% of the subfields contained FOE information, standard deviations of reprojection error were 5.7 deg for macaques and 1.5 deg for humans. Gaze was most influenced by the FOE location from about 250 ms before, with the majority of temporal information being integrated by 800 ms but lasting up to 2 s. Spatial integration was confined to ±4 deg near the gaze location. When another 45% of the subfields were consistent with the motion of a second, independent FOE (with differently colored dots), subjects could still track the FOE of one flow field with a similar profile of temporal integration. The paradigm provides an intuitive and easy to learn framework that can reveal the spatiotemporal profiles of motion integration during continuous behavior, and can be extended to study dynamic selection of information.

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Poster

601. Sensorimotor Transformation: Neurophysiology

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Title: Membrane properties of lamprey lateral pallial neurons and their sensory input - dissecting the primordial cortical microcircuit

Authors: *S. MYSORE SURYANARAYANA, B. ROBERTSON, P. WALLEN, S. GRILLNER;
Karolinska Institutet, Stockholm, Sweden

Abstract: The lateral pallium, corresponding to cortex in mammals, is remarkably conserved in terms of its efferent connectivity, and electrical microstimulation of circumscribed regions evokes eye and orienting movements, movements of the mouth, and in some cases, locomotion (Ocaña et al., 2015). Pallium consists of an outer molecular layer and an inner cellular layer which contains neurons that extend their spiny dendrites into the molecular layer and with an axon that projects out of pallium. The larger of these neurons are glutamatergic and there is also a seperate population, which is GABAergic. One of our goals here is to investigate the active and resting membrane properties of these neurons. Whole-cell patch recordings revealed characteristics of action potentials and after-hyperpolarizations, with post-inhibitory rebound spikes in some neurons. Regular spiking neurons, with fast and slow adapting categories, with two subtypes of the slow adapting. One subtype with low input resistance and a slow firing rate and the other with higher input resistance and a faster firing rate. Intracellular labelling revealed two different morphological types – one with two primary spiny dendrites, which proceeded to the outer molecular layer and branched extensively. These two dendrites were spatially separated enabling them to sample input from different regions of the molecular layer. The axons exited either dorsally or ventrally, presumably part of the dorsal palliopallial (intratelencephalic) tract or the extratelencephalic ("pyramidal") tract, respectively. The other morphological type showed a single primary dendrite, which branched extensively in the molecular layer. With respect to interneurons, GABA and calbindin expressing cells are present. An extensive network of fibers was observed to express somatostatin, but no somata were labelled. Sensory input to the lateral pallium, mainly olfactory, bypasses the thalamus as in mammals and is relayed in two ways – direct input and via the relay nucleus, the *dorsomedial telencephalic nucleus* (dmtn), both of which terminate in distinct layers in the outer molecular layer. Visual input from the retina is relayed to pallium via the thalamus and in addition processed visual information also reaches thalamus via tectum. Taken together, our data suggests that the efferent and afferent *bau-plan* of the cortex is ancient; it had already evolved when the lamprey diverged from the main vertebrate line 560 million years ago. These findings represent the first report of cellular properties in the primordial cortical microcircuit.

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Poster

601. Sensorimotor Transformation: Neurophysiology

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Topic: D.05. Visual Sensory-motor Processing

Support: DFG clinical research group KFO219

Title: Functional cerebral networks of prepulse inhibition: A positron emission tomography (PET) study in freely moving rats

Authors: *C. ROHLEDER[1,2], B. NEUMAIER[2], A. DRZEZGA[3], R. GRAF[4], F. LEWEKE[1], H. ENDEPOLS[2,3];
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Abstract: So far, functional neural networks have been solely described in sedated or fixated animals. Therefore it cannot be precluded that these data are influenced by sedation or high stress levels. However, this disadvantage can be bypassed by conducting behavioral 2[^{18}F]fluoro-2-deoxyglucose (FDG) PET measurements. We have used this innovative technique to further analyze the functional neuronal networks that are active during prepulse inhibition (PPI) of the acoustic startle response. After intraperitoneal injection of 2 mCi FDG, rats (n = 19) were placed in the startle apparatus (San Diego Instruments) and a classical acoustic PPI-paradigm was applied (test condition) for 45 min. On another day rats were solely exposed to 45 min continuous background noise (control condition, resting state). During the behavioral paradigms FDG accumulated in energy-consuming brain cells. Afterwards rats were anaesthetized and a PET-scan (Focus 220, Siemens) was conducted for 30 min. A seed-based correlative network analysis was done with intensity normalized, intra-individual difference images of both behavioral conditions (control minus test condition). Positive correlations indicate that the respective voxel accumulated FDG analog to the seed region, while negative correlations represent inverse relations. We selected 5 different seeds (6-8 voxels each) according to the following criteria: a) Significantly higher FDG uptake during PPI (versus resting state): Auditory cortex (A1), pedunculopontine tegmental nucleus (PPTg) / cuneiform nucleus (CuN), and ventral tegmental area (VTA). b) Significantly lower FDG uptake during PPI: retrosplenial cortex (RSC), c) Correlated to the number of PPI events: prelimbic cortex (PrL). Correlational analysis revealed 3 separate networks: 1) RSC correlated voxels comprised the default mode network. 2) Both A1 and PrL correlated voxels yielded a lateral network including the auditory pathway, insular cortex, amygdala, and ventral hippocampus. 3) A medial network was observed with both PPTg/CuN and VTA seeds, covering cingulate cortex, nucleus accumbens, superior colliculus as well as dorsal hippocampus. Areas appearing in both networks were PrL and PPTg/CuN. Our results suggest that the previously defined PPI modulation network consists of two separate functional units (medial and lateral network), which are connected through key areas of PPI modulation (PrL) and PPI mediation (PPTg/CuN). Both networks are active during passive PPI sessions, while the default mode network is active during resting state.

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Poster

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Topic: D.05. Visual Sensory-motor Processing

Support: HHMI

Title: Control of midbrain motor output by the basal ganglia

Authors: ***E. A. STUBBLEFIELD**[1,2], J. ESSIG[2], G. J. MURPHY[1], G. FELSEN[2], J. T. DUDMAN[1];
[1]Neurosci., Janelia Res. Campus, Ashburn, VA; [2]Physiol. & Biophysics, Univ. of Colorado Sch. of Med., Aurora, CO

Abstract: Orienting to salient stimuli is a fundamental, voluntary behavior. Several lines of evidence have implicated the projection from the substantia nigra pars reticulata (SNr) to the superior colliculus (SC) (i.e., nigrotectal neurons) in mediating this behavior. While most previous research, and models of basal ganglia-midbrain function, have focused on the "uncrossed" input from the ipsilateral SNr to the SC, the anatomy and physiology of "crossed" nigrotectal neurons have recently been described as well. However, whether these classes have distinct functional roles in generating, and perhaps specifying, orienting movements, is unclear. To address this question, we have developed a virtual orienting task in head-fixed mice. Briefly, the mice are trained to move a rotating wheel either to the left or to the right with their forelimbs to bring an eccentric visual stimulus (that initially appears either to the left or right of center) into the center of their visual field via a closed-loop system. Mice move the wheel/bar in the correct direction 85% of the time when the luminance of the bar is high; the percentage of correct movements decreases to near chance levels as the luminance of the visual decreases. *In vivo* recordings are made from identified uncrossed and crossed nigrotectal neurons in mice performing this task. Specifically, we use transgenic mice in which GABAergic neurons of the SNr express ChR2 and optogenetically stimulate one SC hemisphere while performing extracellular recordings of isolated single units from either the ipsi- or contralateral SNr in order to "tag" specific nigrotectal projections with action potential backpropagation. This awake, behaving, cell-type specific recording approach will allow us to elucidate the functional roles of the uncrossed and crossed nigrotectal neurons in mediating orienting movements.

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Poster

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Title: Neural correlates of visually-guided behavior in mouse cingulate cortex

Authors: ***N. A. STEINMETZ**[1], C. P. BURGESS[1], C. ROSSANT[1], S. N. KADIR[1], M. L. D. HUNTER[1], D. F. M. GOODMAN[2], M. CARANDINI[1], K. D. HARRIS[1];
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Abstract: Little is known about the cortical microcircuits underlying cognitive behaviors such as making decisions among multiple alternatives. In mice, a cortical area that may perform computations underlying these behaviors is the cingulate cortex (Cg). This midline area exhibits visual responses and reciprocally connects with primary visual cortex (V1) and superior colliculus, among other areas. To understand the role of the Cg in visually-guided behaviors, we trained mice to perform a 3-alternative visual discrimination task and used next-generation microelectrodes to simultaneously record millions of spikes from hundreds of neurons. In the task, mice were shown gratings of varying contrast located to the mouse's left and/or right. The mouse could earn a water reward by selecting the correct response: turn a wheel clockwise if the grating on the left was present and had higher contrast than that on the right; turn counterclockwise if the reverse was true; or refrain from responding for 1.5 seconds if no grating was shown. Mice learned this task well, performing at >66% accuracy (and often much higher) on trials with high contrast stimuli or no stimuli (chance = 33%). While mice performed the task,

we recorded in the Cg or, for comparison, from V1. Recordings were made with 128-channel silicon microelectrodes fabricated by IMEC, allowing for the simultaneous recording of more than 200 isolated neurons in a small region. The unprecedented magnitude of these datasets (>5 million spikes, with individual spikes appearing on up to 12 sites) required new software for the automatic and manual stages of spike sorting, including new versions of KlustaKwik and KlustaViewa. For each neuron, we quantified its responses to the visual stimuli, to the auditory "go cue", to the execution of wheel turns, and to the delivery of positive or negative feedback. A majority of Cg neurons responded significantly to at least one of these task events, and many responded to more than one, indicating a mixed representation. By comparison, in a limited sample of V1 neurons, many responded to visual stimuli, but none responded to the go cue, to the execution of the wheel turns, or to feedback. Finally, we characterized whether the neurons represented the choice of the mouse, independent of the actual stimulus conditions. Only a small fraction of Cg neurons, and no V1 neurons, represented the decision. In summary, the Cg contains neurons representing each aspect of the behavioral task, but only a very sparse subpopulation of its neurons seemed to represent the decision or motor response. Whether and how this population of neurons contributes causally to the performance of the task awaits future experiments.

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Poster

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Support: MRC Grant - MR/K500902/1

Title: Fronto-cortical projections to medial and lateral subdivisions of the mouse Superior Colliculus and their potential role in approach and avoidance behaviour

Authors: *M. A. SAVAGE, R. MCQUADE, A. THIELE;
Inst. of Neurosci., Newcastle Upon Tyne, United Kingdom

Abstract: Different types of orienting behaviour require coordination of activity in many different cortical and subcortical areas. It has been shown that the Superior Colliculus (SC)

processes information regarding current goal directed behaviours, and a recent study in rats has suggested that there is a segregation of avoidance and approach behaviours along the medial (m) and lateral (l) divide of the SC. Here we investigate the connectivity of these subregions of the SC with upstream structures associated with orienting behaviours in the mouse. The retrograde tracer Fluorogold (FG) was iontophoresed into the SC(l) or SC(m) of anaesthetised mice. In a separate group, the anterograde tracer biotinylated dextran amine (BDA), was pressure injected either into motor cortex area 2 (M2) or the cingulate area (Cg). 3-4 days post injections the animals underwent cardiac perfusion with paraformaldehyde, and the brains were frozen and 40 µm coronal sections collected. FG retrograde tracer was visualised after incubating with an anti-FG antibody (Millipore AB153I) followed by amplification with biotin and strepavidin Alexa 488. BDA anterograde tracers were visualised by incubation with strepavidin Alexa 488. Tracer signals were mapped onto representative brain atlas images from Franklin & Paxinos. Retrograde tracing: Almost all cortical sensory areas projected to the SC in general, as well as the thalamus and the substantia nigra. The lateral and medial subregions do indeed have differing connectivity profiles, with SC(m) receiving more input from visual areas and areas involved in autonomic responses. Conversely SC(l) receives more somatosensory and whisker based inputs. The prefrontal area of motor cortex 2 (M2) was highly labelled with tracer from SCl (layer 5). The Cingulate cortex (Cg) was labelled more strongly after SCm injection (layer 5). Anterograde tracing: M2 projects to a variety of cortical area, with a preference to somatosensory areas (S1), motor output areas, motor area 1 (M1), and SC(l) compared to SC(m). Cg sends connections to visual area 1 (V1) and the amygdala. Following Cg injections anterograde labelling was much stronger in the SC(m) than in the SC(l). The results presented here are consistent with the known connections which exist onto the SC in other species (e.g. rat). Furthermore the area of highest activation, frontal M2, which appears to be similar to orienting areas characterised in rats, represents an interesting region/area for further study. Cg has also been implicated in orienting behaviours in rats. The different distributions from SCm/l to Cg/M2 are likely to underlie specific types of orienting behaviour relating to avoidance and approach.

Disclosures: **M.A. Savage:** None. **R. McQuade:** None. **A. Thiele:** None.

Poster

601. Sensorimotor Transformation: Neurophysiology

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Topic: D.05. Visual Sensory-motor Processing

Support: NIH R01 EY022854

NIH R01 EY024831

Title: Multi-channel recording in the superior colliculus - insights into network computation and communication

Authors: *U. K. JAGADISAN, N. J. GANDHI;
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Abstract: The superior colliculus (SC) is one of the most thoroughly studied structures in the brain. Although we know a substantial amount about SC function and its role in mediating sensorimotor transformations through gaze shifts, questions abound about the exact mechanisms by which these transformations are implemented. Furthermore, it is unclear how SC's role in producing gaze shifts meshes with its purported role in processes such as attention, target selection, and post-saccadic feedback, although dynamic information processing within SC and between SC and cortical structures has been hypothesized to play an important role in these functions. These unresolved issues are in part due to the limitations of the traditional approach of recording with single microelectrodes from individual SC neurons. For example, by recording from only a single site in the intermediate layers of the SC, one is left to infer how inter-laminar information flow and feedback in an SC column guide even the simplest of sensorimotor behaviors. To study SC function in finer detail, we combined linear microelectrode array recordings with multi-channel signal analyses. Linear arrays are especially amenable to recording from within a column of neurons to obtain snapshots of the computations evolving in parallel within the column. We recorded from the SC in two rhesus macaques (Macaca mulatta) performing simple oculomotor tasks. The electrode contacts (n=16) spanned the dorso-ventral extent of the SC, allowing for the simultaneous recording of spiking activity and local field potentials (LFPs) from the superficial through the intermediate and deeper layers. Noise correlations between pairs of task-related neurons were low or negative compared to typical values in the cortex, consistent with the idea that the network becomes uncorrelated as you get closer to the end of a sensorimotor decision chain. We have also begun to analyze cross-channel spike-spike coherence (cross-correlations) and spike-LFP coherence and examine the relationship between the neurons' functional properties based on firing rate (e.g., visuomovement index) and their contributions to dynamic information processing in the SC network.

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Poster

601. Sensorimotor Transformation: Neurophysiology

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ORIP ODO10425

Research to Prevent Blindness

Title: The reliance of FEFsem activity on retinal input

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Abstract: Primates are highly skilled at foveating moving objects through smooth pursuit (SP) eye movements. These eye movements require the integration of both retinal and extra-retinal signals. Although a growing body of work has shown that the smooth eye movement subregion of the frontal eye fields (FEFsem) is involved in generating voluntary SP, the relative contributions of retinal and extra-retinal signals to FEFsem activity remain an open question. To assess the dependence of the FEFsem on retinal input, we recorded 72 neurons in 3 monkeys during a step-ramp paradigm. We tested two types of visual perturbations: target blink and large-field (LF) background. In the first condition, the target was blinked off for 150 ms at 50, 100, 200, 300, 400, or 500 ms after ramp onset. Neuronal response was measured over a 150-ms interval, 60 ms after blink onset, and compared to the same interval in control trials (no blink). In the second condition, a LF background was moved with the target and neuronal response over the ramp interval was compared to control. Neuronal latency was estimated, and contributions of visual motion and eye motion were assessed using multiple linear regression modeling. Of the 33 neurons tested with target blinks during SP initiation (blink at 50 or 100 ms), 8 had a FR less than 60% of control FR, 18 had a FR greater than 90% of control. Of the 70 neurons tested with target blinks during maintenance (blink at 200, 300, 400, or 500 ms), 2 had a FR less than 60% of control, while 49 had a FR greater than 90% of control. To probe the basis of these differences in response to target blink, we compared the neuronal latency, and eye and visual motion sensitivity as estimated by linear regression. For neurons tested with target blinks during initiation, there was no significant difference between neurons that had FR decreases below 60% of control and those whose FR was above 90% of control. When tested with LF motion, the majority of neurons (16/21) showed an increase in FR when compared with control, and 9 of those showed a FR greater than 125% of control. Only 2 neurons showed a decrease in FR below 75%. Neurons that increase their FR above 125% of control show significantly shorter neuronal latencies than those cells that did not ($p<.002$). These results suggest that neuronal dependence on retinal signals may not be consistent throughout the FEFsem, or even over time for a particular cell. Whether neuronal populations differing on these measures underlie distinct

functions remains unknown. Further work to elucidate the relationship between these characteristics and FEFsem projections is ongoing.

Disclosures: L.R. Bakst: None. **J. Fleuriet:** None. **M.J. Mustari:** None.

Poster

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Topic: D.05. Visual Sensory-motor Processing

Support: R01-EY017366

Title: Robustness of direction discrimination performance during LIP inactivation

Authors: *L. N. KATZ, J. L. YATES, A. C. HUK;
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Abstract: Neural correlates of the accumulation of evidence have been repeatedly observed in the average firing rates of neurons in the lateral intraparietal area (LIP). We tested whether this decision-correlated activity has a causal role by recording and then reversibly inactivating LIP neurons in two macaques performing multiple variants of a motion discrimination task. Neural activity was recorded before and during muscimol infusion with multisite linear electrode arrays. LIP was identified by strong contralateral delay-period activity across the array during an instructed saccade task. During muscimol infusion we recorded electrophysiological silencing of neural activity across the array channels, consistent with a >2mm inactivation (radius) within LIP, centered on choice-selective patches. LIP inactivation produced reliable behavioral effects in a free-choice task where reward was given for saccades to either of two targets, equally. Following inactivation, free choices were biased away from the inactivated field by 13% and saccade accuracy to the inactivated field was decreased (23% increase in endpoint scatter). Given both electrophysiological and behavioral confirmation of LIP inactivation, we then evaluated the effects of inactivation on motion discrimination performance. We found no measurable effect of LIP inactivation on either slope, inflection or lapse-rate of the psychometric function when one target was placed in the inactivated field (6012 trials over 13 sessions). Varying the spatial configuration of the task by placing both targets within the inactivated region produced no effect either (1516 trials, 3 sessions). We further varied the temporal structure of the standard task to test whether limiting motion evidence available to the macaque would increase the behavioral dependence on LIP signals. Motion duration was varied between 150 msec to 1 sec on each trial

but we found no reliable effect on neither psychometric parameter describing choice behavior (5008 trials, 3 sessions). We also explored LIP inactivation of simple visual responses, instead of focusing on decision-correlated activity. We placed the motion stimulus in the inactivated region and positioned targets ipsi-lesionally, which produced a small but non-significant effect on choices (2006 trials, 4 sessions). Taken together, these results limit the range of proposed roles for LIP function in decision making. If decision signals in LIP play a causal role in perceptual decision-making, the means by which choice-related activity is represented and/or read-out may involve far more flexible and spatially-widespread mechanisms than those typically asserted.

Disclosures: **L.N. Katz:** None. **J.L. Yates:** None. **A.C. Huk:** None.

Poster

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McGovern Institute for Brain Research

Title: Response of neurons in the medial prefrontal cortex during a time interval integration task

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Abstract: Complex behaviors often require sensitivity to temporal contingencies between stimuli and actions. To play an instrument, for example, the musician must continuously track the note durations while anticipating the upcoming beats. Internal variability, however, limits performance in tasks that require tracking the passage of time. We previously found that humans reduce this variability by both (1) incorporating information from prior experience and (2) integrating multiple measurements when possible (Egger and Jazayeri, 2014). However, the neuronal basis of these computations is not understood. To characterize the underlying neural mechanisms, we trained a monkey to perform a time interval integration and production task. In each trial, the animal was presented with three flashes of light (1, 2 and 3), demarcating two identical intervals (between flashes 1 and 2, and 2 and 3). Across trials, the interval between flashes was randomly sampled from a uniform distribution between 600 and 1000 ms. The

animal was required to measure the interval and reproduce it as accurately as possible with either a saccade or a manual lever press immediately following the 3rd flash. As in humans, the monkey's production intervals were biased toward the mean of the interval distribution, suggesting they used prior information in interval estimation. Moreover, the animal integrated the two measurements with approximately equal weights as indicated by the analysis of behavior in randomly interleaved probe trials in which the two sample intervals were slightly different. Overall, the monkey's behavior was consistent with the predictions of a Bayesian model that optimally integrates the two measurements with the prior distribution of sample intervals. While the monkey performed the interval integration task, we recorded single and multiunit activity in the medial prefrontal cortex, which is thought to play a key role in time perception and production. Some neurons exhibited responses predicted by previous observations such as ordinal selectivity, motor related bursts or response monitoring. Other neurons responded with ramping activity during the measurement and/or production epochs of the task. Interestingly, some of these neurons responded with different ramping activity between the two measurement epochs, indicative of a possible role in measurement integration. Taken together, these results suggest medial prefrontal neurons contribute to a broad basis of high-level functions necessary to perform the task: keeping track of the flash number, integration of measured intervals, preparation for interval reproduction and monitoring the outcome.

Disclosures: S.W. Egger: None. **C. Chang:** None. **M. Jazayeri:** None.

Poster

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Topic: D.05. Visual Sensory-motor Processing

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Title: Neural correlates of multimodal arm position estimation in the posterior parietal cortex

Authors: *P. VANGILDER, JR, Y. SHI, G. APKER, C. A. BUNEO;
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Abstract: In order to improve neural prosthetic design, as well as to fully understand the neural correlates of arm position estimation, it is imperative that we understand how visual and

proprioceptive information interact in arm movement-related regions of the brain. Previous work in monkeys has shown that during the active maintenance of arm positions in 3D space, visuo-proprioceptive integration is associated with suppression of neural firing rates as well as reduced intratrial and across-trial neural variability in the posterior parietal cortex (PPC). To further explore the nature of integration induced changes in variability we compared the spike train and local field potential dynamics in the PPC as animals held their arm at multiple spatial locations while receiving either unimodal (proprioceptive) or bimodal (visuo-proprioceptive) feedback on a pseudorandom basis. Neurons were classified as Poisson, bursty, refractory or oscillatory based on their spike train power spectra and autocorrelograms. Forty percent of the neurons were classified as oscillatory in a 13-30 Hz frequency band in either unimodal and bimodal conditions or both. Significant spike-field coherence was common in this population of cells and under bimodal conditions the incidence of coherence was significantly greater than in cells without oscillatory spiking activity. The results suggest the presence of a temporal code for multimodal information in the PPC during the control of action, which may have important implications for the cortical representation of body schema.

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Poster

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Center for the Neural Basis of Cognition

Title: Congruence of spatial selectivity for local field potentials and spiking activity in primate posterior parietal cortex

Authors: ***N. J. HALL**[1,3], R. J. GERTH[2,3], C. L. COLBY[1,3];
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Abstract: A large body of evidence shows that the responses of single neurons in primate posterior parietal cortex are spatially selective. Modulations in the firing rate of individual

neurons reflect an output signal from the neuron. But what about the incoming synaptic activity that drives these neural responses? The synaptic input is thought to be reflected in local field potentials (LFP), which are low frequency fluctuations in the extracellular voltage. We asked whether LFPs are also spatially selectivity. We recorded in area LIP and adjacent parietal cortex in awake behaving monkeys. We used an 8-channel linear array electrode to measure LFPs and single unit activity simultaneously. We found that LFPs are spatially selective. Further, the spatial selectivity is congruent with that of the local single unit activity. These findings are consistent with previous observations on LFPs in parietal cortex (Hagan et al., 2012; Mirpour and Bisley, 2013). Recordings were carried out while the macaque performed a memory guided saccade task. During the task, the animal must perceive a briefly flashed visual stimulus, remember the location of the stimulus, then plan and execute a saccade to the remembered location. This task allows for the temporal separation of neural activity in response to the visual stimulus and saccade execution. Parietal neurons are spatially selective for visual responses and eye movements. Response fields for single neurons are typically at matched locations for each task epoch. We found that LFPs are likewise spatially selective for corresponding locations in each task epoch. We conclude that LFPs and spiking activity have congruent spatial selectivity.

Disclosures: **N.J. Hall:** None. **R.J. Gerth:** None. **C.L. Colby:** None.

Poster

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Title: Evoked movement vectors of cortical motor fields in primates

Authors: ***D. J. MILLER**, R. M. FRIEDMAN, I. STEPNIEWSKA, J. H. KAAS; Psychology, Vanderbilt Univ., Nashville, TN

Abstract: The sensorimotor networks underlying coordinated movement useful in neural interfacing systems designed to restore motor behavior extend from primary sensory areas through the parietal lobe and into the frontal cortex. Long train intracortical microstimulation (ICMS) has been used to show the presence of classes of movements within important nodes in

this sensorimotor network, such as primary motor (M1) cortex of the frontal lobe and posterior portions of the parietal lobe (PPC; Stepniewska et al., 2005, 2009). Classes of movements evoked with ICMS are also preferentially connected across brain regions and this circuitry has been shown to mediate specific motor behaviors (Gharbawie et al., 2011). However, the local organization of movements is fractured within the broader movement domains which exhibit a rough somatotopy, making it difficult to determine the contributions these neurons make to coordinated movement. In this project, we investigate the local organization of evoked movement vectors (EMV) within domains in M1 and PPC in prosimian galagos and new world squirrel monkeys. Our data indicate that EMVs from M1 and PPC are highly consistent across individuals and exert excitatory or inhibitory effects upon EMVs from sites in similar or distinct movement domains, respectively. In addition, these results suggest that neurons in these cortical motor fields function in reference to coordinate frames dependent upon proprioceptive input as many EMVs in M1 and PPC show an effect of starting position. These data may help explain motor behavior by providing evidence suggestive of an organizing principle of cortical motor field physiology.

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Poster

601. Sensorimotor Transformation: Neurophysiology

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Topic: D.05. Visual Sensory-motor Processing

Support: Richard A. Andersen

Defense Advanced Research Projects Agency

Title: An internal model for reaching using sensorimotor transformations

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Abstract: Traditional accounts of visually guided reaching assume that the purpose of sensorimotor computation is to transform representations of reach targets, i.e. the desired final limb position, from visual coordinates into motor coordinates. However, behavioral and neurophysiological studies have increasingly challenged predictions of this movement-planning

framework. As an alternative, I present a model of sensorimotor processing that generates an internal representation of limb kinematics. Simulations show that a network model based on this hypothesis generates population responses consistent with those in reach-related areas of monkey posterior parietal cortex (PPC). In particular, the model provides an explanation for the puzzling phenomenon of intermediate reference frames commonly found in sensorimotor cortex. These results suggest that although sensorimotor representations are typically studied in the moments preceding movement, their proper interpretation requires a consideration of the movement itself.

Disclosures: C. Ustun: None.

Poster

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Title: Visuo-motor processing of objects in pre-supplementary motor area F6 neurons of the macaque

Authors: *L. BONINI[1], A. LIVI[2], M. LANZILOTTO[2], M. MARANESI[1], P. RUTHER[3], F. BARZ[3], L. FOGASSI[2], G. RIZZOLATTI[1];
[1]Italian Inst. of Technol. - BCSMC, Parma, Italy; [2]Univ. of Parma, Parma, Italy; [3]Dept. of Microsystems Engin. (IMTEK), Univ. of Freiburg, Freiburg, Germany

Abstract: Area F6 underlies several high-order motor control functions, such as the learning of new motor sequences, task switching, and the temporal structuring and ordering of forthcoming behaviours based on sensory stimuli, in particular of forelimb actions. Indeed, anatomical studies suggest that F6 constitutes a bridge between prefrontal cortex and the ventral (F5c/p) and dorsal (F2) rostral premotor areas involved in the control of hand and arm motor actions. However, the possible contribution of area F6 neurons to the control of natural limb actions is poorly understood. To fill this gap, here we recorded F6 neurons activity by means of chronically implanted arrays of linear silicon-based multielectrode probes from one monkey while it was performing a visuomotor task including two main (randomized) conditions: one required the

monkey to grasp a target object (action), the other to remain still for the entire duration of the trial (inaction). Each trial started when the monkey engaged fixation in complete darkness. A cue sound instructed it either to grasp (high tone - action) or simply to fix (low tone - inaction) the subsequently presented target. After 800 ms a light switched on, revealing one among three different graspable objects (target presentation). At the end of the sound (go/no-go signal), the monkey had to reach, grasp and pull the object (0.8 s - action), or to remain still (1.2 s - inaction). We recorded 89 task-related neurons. Most of them (78%) showed sensory-evoked activity during the presentation of sensory stimuli, particularly object presentation during go relative to no-go trials, often (32%) followed by motor-related activity. The remaining neurons (22%) discharged only during action preparation/execution, or during the inaction phase. Interestingly, almost half of the visually-responsive neurons showed object-selective activity: when tested with a plastic barrier interposed between the monkey's hand and the object, which typically reduces object presentation responses of area F5 neurons, F6 neurons visual responses remained similar to those evoked by the presentation of the same object during no-go trials. These findings demonstrate that, besides being related to the selection and triggering of intentional actions, area F6 neurons can also show object/grip selectivity. As compared to area F5 neurons, which encode object properties in terms of the potential motor action afforded by it, area F6 neurons seem to encode object properties depending on whether the monkey will actually grasp them.

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Poster

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METR (ΑΡΙΣΤΕΙΑ II)

LATSIS FOUNDATION

Title: Mirror neurons respond to the observation of intransitive actions

Authors: *V. PAPADOURAKIS[1,2], V. RAOS[1,2];
[1]Univ. of Crete Med. Sch., Iraklion, Greece; [2]Inst. of Applied and Computat. Mathematics, Fndn. for Res. and Technol. - Hellas, Iraklion, Greece

Abstract: According to the original description by Rizzolatti and colleagues, the prerequisite of triggering the discharge of mirror neurons (MNs) is the interaction of the hand with an object. On the other hand, several studies reported that the MN system in humans can be activated also by non object-directed (intransitive) movements. This difference between human and monkey MN systems has been considered to reflect an evolutionary step. A recent study reported that 73% of MNs recorded were responding to the observation of a pantomimed action, but no other data were provided. Moreover, neuroimaging studies in monkeys revealed that observation of intransitive actions activates the ventral premotor area F5. To resolve this discrepancy MNs were recorded from ventral premotor area F5 while the monkeys observed transitive and intransitive actions. Initially, the monkeys were trained to reach for and grasp 3D objects with the appropriate grips. At the beginning of each trial, a LED above the selected object turned on and the monkey had to fixate it and press a key. Following a fixation period, a dimming of the LED signaled the onset of the reach-to-grasp movement. The monkey had to reach for, grasp, pull and hold the object while fixating it until the extinction of the LED cuing its release. Then, the monkeys were trained to observe the experimenter employing the same object-directed reaching-to-grasp actions, as well as an out-reaching non-goal-directed movement with extended wrist and fingers towards the location where the object was placed during the transitive actions, while maintaining its gaze straight ahead. During observation, no cuing LED was visible to the monkey and the experimenter was getting instructions on a screen out of the monkey's view. The experimenter was standing next to the animal on its right side, and both reaching and grasping components of his movement were visible to the monkey. Out of the 216 MNs recorded, 197 responded to the observation of both transitive and intransitive actions. The discharge to both transitive and intransitive actions initiates with movement onset. The response peak occurs around 70% and 50% of the movement duration for transitive and intransitive actions, respectively. Furthermore, discharge rate for the intransitive actions is 30% and 10% lower than the response to the preferred and not-preferred transitive action, respectively. Finally, responses elicited by intransitive movements, last 60% less than those evoked by transitive ones. These results resolve the long lasting discrepancy on the stimuli triggering the monkey and human MN systems and dictate a reevaluation of the mechanism through which their functions are sub-served.

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Poster

601. Sensorimotor Transformation: Neurophysiology

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Topic: D.05. Visual Sensory-motor Processing

Title: State-dependent impact of transcranial alternating current stimulation of the motor mirror system

Authors: *M. FEURRA[1], M. NAZAROVA[2], E. BLAGOVESHCHENSKY[2], M. YUREVICH[2], A. LEBEDEVA[2], D. POZDEEVA[2], V. NIKULIN[3];
[1]Natl. Res. University, Higher Sch. of Ec, Moscow, Russian Federation; [2]Natl. Res. University, Higher Sch. of Econ., Moscow, Russian Federation; [3]Univ. Med. Berlin, Dept. of Neurol. and Clin. Neurophysiology., Berlin, Germany

Abstract: Recent evidence showed that Transcranial Alternating Current Stimulation (tACS) entrains the endogenous cortical oscillatory activity with a frequency and state-dependent specificity. In a previous study we showed state-dependent effects of tACS delivered on the primary motor cortex (M1) during a motor imagery task. The theta and alpha-tACS increase of corticospinal excitability, respectively indicated a reinforcement of working memory processes required to mentally process and "execute" the cognitive task and a synchronization of alpha oscillatory attentional patterns commonly associated with visual imagery. Here we adopted the same experimental setup to test state-dependent effects of tACS during action-observation, a cognitive task which produces the activation of the mirror motor system that simulates what would happen if the observer would execute himself a not goal-directed pinch-to grip action. Motor-evoked potentials (MEPs) were obtained by transcranial magnetic stimulation (TMS) of M1 by using an online-navigated TMS-tACS setup. Preliminary data showed that beta-tACS confirmed to increase M1 corticospinal excitability of subjects at rest. During action observation, the increase of corticospinal excitability was maximal with alpha-tACS, likely reflecting hypothesis that the mu rhythm in alpha range may specifically index downstream modulation of primary sensorimotor areas by mirror neuron activity and appear to reflect the translation of perception into action. Interestingly the absence of theta-tACS enhancement might reflect a lack of working memory engagement which is crucial for visual motor imagery. Our findings help to disentangle similarities and differences between motor imagery and action observation in terms of frequencies specificity and confirmed that tACS could be used to induce state-dependent enhancement effects.

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Poster

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OGSST

Title: Visual feedback modulates functional connectivity between anterior intraparietal sulcus and ipsilateral motor cortex

Authors: *G. JEGATHEESWARAN[1,2], M. VESIA[1], R. ISAYAMA[1,2], R. CHEN[1,2];
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Abstract: Background: Mirror therapy, an intervention used to treat stroke-related motor dysfunction, uses visual feedback of an active unimpaired limb from a mirror to restore function in an impaired limb. Transcranial magnetic stimulation (TMS) studies suggest that the motor cortex (M1) ipsilateral to the moving hand is activated with mirror visual feedback. The mechanisms underlying this feedback are not well understood. However, with these illusory movements, the mirror neuron system involving neural structures in the parieto-frontal areas are thought to play a role. The anterior intraparietal sulcus (aIPS), in particular, is activated during action observation of a grasping movement. **Purpose:** The purpose of this study is to determine if aIPS causally influences the activity of ipsilateral M1 during movement preparation with mirror visual feedback. **Hypothesis:** We hypothesized that the aIPS-M1 functional connectivity will be modulated by mirror visual feedback. **Methods:** Eight healthy subjects (4 females and 4 males) participated and were tested in 4 randomized conditions: mirror (subjects looked at a mirror where they saw the right hand as an illusory left hand), no-mirror (subjects looked at an opaque board in place of a mirror), action observation (AO; subjects watched a video of a left hand while both their hands were at rest) and rest (subject looked at a mark placed in the centre while both hands were at rest). In the first two conditions, subjects were instructed to grip a force transducer with their right finger and thumb after an auditory "Go" signal. The subjects held the grip with 20% of their maximum voluntary contraction. TMS pulses were delivered before the grip through two coils placed on the right hemisphere separated by 2, 4, 6, 8 or 10 ms; the first pulse over the aIPS (90% resting motor threshold) and the second pulse over the M1 (1 mV). Motor evoked potentials (MEPs), were recorded from the resting left first dorsal interosseous muscle. **Results:** aIPS-M1 MEP ratio was facilitated in the mirror condition compared to rest at 4 ms ($P = 0.03$). Specifically, the MEP ratios (<1 means inhibition, >1 means facilitation) for rest, mirror, no-mirror and AO conditions at 4 ms were: 0.76 ± 0.24 (mean ± SD), 1.02 ± 0.37,

0.95 ± 0.31 and 1.15 ± 0.27, respectively. **Conclusions:** Findings suggest that the aIPS-M1 functional connectivity differed among the conditions at a specific time interval of 4 ms (rest vs. mirror). These findings provide further causal evidence that aIPS-M1 interactions can be modulated by mirror visual feedback.

Disclosures: G. Jegatheeswaran: None. **M. Vesia:** None. **R. Isayama:** None. **R. Chen:** None.

Poster

601. Sensorimotor Transformation: Neurophysiology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 601.18/L40

Topic: D.05. Visual Sensory-motor Processing

Support: Suzuken

Takeda

Title: Enhanced human motor cortical plasticity by combined mirror visual feedback therapy and transcranial direct current stimulation (tDCS)

Authors: *Y. UEKI[1], M. HORIBA[1], Y. SHIMIZU[1], K. SAHASHI[1], K. ITO[1], J. MIZUTANI[1], I. WADA[1], N. MATSUKAWA[1], I. NOJIMA[2];
[1]Nagoya Citiy Univ., Nagoya, Japan; [2]graduate school of medicine, Nagoya university, Nagoya, Japan

Abstract: Non-invasive brain stimulation including transcranial magnetic stimulation and trans direct current stimulation (tDCS) has been shown to modulate brain processing and cortical plasticity non-invasively, which influence human motor behavior. Neuroplasticity based intervention including training and brain stimulation are promising strategy for facilitating motor skills learning. However, it remains unclear whether motor skill learning combined with tDCS induces robust plasticity in human primary motor cortex. To clarify this, we investigated changes motor cortical plasticity associated with the different stage of motor skill learning combined with mirror visual feedback therapy and tDCS. Subjects (Twelve healthy aged volunteers) participated in combined therapy twice on separated days. In Day 1 (early learning condition), they practiced ball rotation task of left hand with mirror visual feedback approach with tDCS or sham. As practice continuing, subjects learned how to rotate the ball and their performance was gradually improve. Seven days after, in Day 2 (late learning condition), they additionally learned the ball rotation with tDCS or sham. To analyze behavioral change, the maximum acceleration and

number of ball rotation of left hand were calculated just before and after the training with tDCS or sham. The motor cortical plasticity was also evaluated using by motor evoked potential. The maximum acceleration and number of ball rotation of left hand were significantly increased both in Day 1 and Day 2 with tDCS compared with sham. In addition, motor evoked potential were significantly increased both in Day 1 and Day 2 with tDCS compared with sham, showing that the combined mirror visual feedback therapy and tDCS induce the cortical plasticity more strongly. In conclusion, combined mirror visual feedback therapy and tDCS is useful tool for inducing motor cortical plasticity during early and late stage of motor learning. This therapy might become new rehabilitation strategy for modulating the brain processing related to the motor skill learning.

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Poster

601. Sensorimotor Transformation: Neurophysiology

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Topic: D.05. Visual Sensory-motor Processing

Support: European Research Council (ERC; ActSelectContext 260424)

Title: A high resolution MEG study of predictive coding in action selection

Authors: ***J. J. BONAIUTO**[1], S. MEYER[2], G. BARNES[2], S. BESTMANN[3];
[2]Functional Imaging Lab., [3]Sobell Dept. for Motor Neurosci. and Movement Disorders, [1]Univ. Col. London, London, United Kingdom

Abstract: Predictive coding accounts suggest that higher cortical regions generate predictive models of the inputs they receive, whereas prediction errors are signalled through ascending connections from lower regions in the hierarchy. One specific hypothesis is that beta oscillations in deep cortical layers are markers of predictions, while prediction errors are reflected in gamma oscillations originating from superficial layers. We used high resolution MEG to test this frequency-specific predictive coding account of action selection. Subjects were first presented with a predictive stimulus (random dot kinematogram with apparent motion to the left or the right at one of three levels of coherence: low, medium, or high). The coherence levels were set for each individual based on their discrimination threshold. After a delay, an imperative stimulus (arrow pointing to the left or the right) required a left or right button press as quickly as possible.

The motion direction of the predictive stimulus was congruent with the imperative stimulus, with three levels of congruency (low, medium, high). The level of congruence thus influenced the strength of the prior expectation in a given context, whereas the level of coherence on a single trial dictated the strength of the prediction about the forthcoming imperative stimulus. Consequently, we reasoned that beta power should scale with motion coherence prior to the imperative stimulus, before the imperative stimulus occurs. By contrast, following the presentation of the imperative stimulus, gamma power should scale with coherence level in incongruent trials, i.e. when a violation of the prediction conveyed by the predictive stimulus occurred. We used subject-specific 3D printed head-casts (Troebinger et al., 2014a) which reduce coregistration and movement error to ~1mm and allow high precision mapping to anatomy (Troebinger et al., 2014b). We found that prior to the imperative stimulus, beta power in primary motor cortex scaled with the motion coherence of the predictive stimulus, consistent with beta oscillations signalling predictions about forthcoming actions. After the imperative stimulus, gamma power increased with decreasing coherence in congruent trials and increasing coherence in incongruent trials, providing support to the proposal that gamma activity encodes the prediction error.

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Poster

601. Sensorimotor Transformation: Neurophysiology

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: D.05. Visual Sensory-motor Processing

Support: R01HD58301

R01NS5085122

Title: Comparison of TMS elicited and voluntary synergies of the human hand

Authors: *M. YAROSSI[1,3], Y. WEI[3], S. ADAMOVICH[3], E. TUNIK[2];
[1]Grad. Sch. of Biomed. Sci., [2]Sch. of Hlth. Related Professions, Rutgers Biomed. Hlth. Sci., Newark, NJ; [3]Biomed. Engin., New Jersey Inst. of Technol., Newark, NJ

Abstract: Evidence in a non-human primate model suggests a small number of synergies, elicited by electrical microstimulation to M1, can capture the variance of EMG activity patterns elicited by grasping objects. The aim of this study was to establish if a similar relationship

between voluntary and elicited synergies can be determined for the human hand using transcranial magnetic stimulation (TMS) to stimulate motor cortical neurons. Five healthy subjects participated following informed consent. Prior to mapping, the first dorsal interosseous motor hotspot and resting motor threshold (RMT) were determined. High density TMS mapping was conducted at 110% of RMT, using neuronavigated TMS applied to a 7x7 cm area centered over the hotspot. EMG was recorded from 8 hand muscles. An elicited activation tuning (Elicited) was derived for each stimulation by determining the MEP amplitude of each muscle. Following mapping each subject performed hand gestures in the American Sign Language alphabet. Voluntary activation tunings (Voluntary) were determined for each sign by calculating the average rectified amplitude of EMG over a 2 second window. For each subject, we used non-negative matrix factorization (NNMF) to identify a set of synchronous muscle synergies underlying the elicited and voluntary EMG data. For a given dimensionality, the algorithms iteratively updated model parameters, until the total reconstruction error was reduced <5% over 10,000 iterations. These synergies were chosen for further analysis. The ability of the NNMF-decomposed synergies to reconstruct the original data from each task was found using a nonnegative least-squares constraint algorithm, and quantified as the one minus the root-mean-square error (RMSR) between the original and reconstructed data. Five or less NNMF-derived synergies were able to account for 93.0±1.2% (Voluntary) and 98.5±1.1% (Elicited) of the variance in the data set from which they were derived, providing evidence of the usefulness of NNMF for dimensionality reduction. Most interestingly, the elicited synergies accounted for 81.2±9.8% of the variance in the voluntary data set. These data provide evidence in a human model, that magnetic stimulation of a distributed M1 territory evokes a small number of synergies equivalent to those found from voluntary movement. This technique may be useful to assess the development of abnormal synergies in pathology, and track hand recovery associated with reduction of abnormal synergistic movement.

Disclosures: **M. Yarossi:** None. **Y. Wei:** None. **S. Adamovich:** None. **E. Tunik:** None.

Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

Location: Hall A

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Topic: D.08. Pain

Support: National Research Foundation (NRF) Grant (2012R1A3A2048834) funded by the Korean Government, Korea

Title: Lysophosphatidylcholine(LPC)-induced pain is medicated by activation of TRPM2 in mice

Authors: P. CHO[1], *J. LIM[1], S. LEE[1], Y. KANG[1], S. OH[2], S. JUNG[1];
[1]Hanyang Univ., SEOUL, Korea, Republic of; [2]Seoul Natl. Univ., SEOUL, Korea, Republic of

Abstract: Lysophosphatidylcholine (LPC) is an endogenous lipid, of which hydrolysis is generally the result of the enzymatic action of phospholipase A2. LPC plays the important roles in the activation of macrophage, demyelinating disease and hyperalgesia and mechanical allodynia in peripheral neuropathy. In neuropathic pain, it was suggested that signaling pathway of LPC was associated with nitric oxide synthase, protein kinase C, or lysophosphatidic acid receptor. However, molecular mechanism of LPC-induced nociception has not been understood. The recent study reported that LPC-induced Ca2+ increase in neutrophil was mediated by transient receptor potential melastatin 2 (TRPM2) ion channel, which is a Ca2+-permeable nonselective cation channel activated by intracellular ADP-ribose (ADPR) and by hydrogen peroxide (H2O2). Thus we investigated whether LPC induce acute nociception, if so, what molecular mechanism is involved in nociception. The intraplantar injection of LPC evoked spontaneous pain behavior (licking and biting) for 30 min and reduced the paw withdrawal latency for 120 min, while LPC-induce nociception in TRPM2 -/- mice was decreased. In whole cell patch clamp, LPC activated the inward current with a biophysical property of TRPM2 and it was abolished by gadolinium and TRPM2 blocker, N-(p-amylcinnamoyl) anthranilic acid (ACA) in mice dorsal root ganglion (DRG) neuron. Taken together, our finding suggest that endogenous lipid, LPC is involved in the acute nociception, which is mediated by the activation of TRPM2 in DRG neuron and LPC/TRPM2 pathway may also be associated with neuropathic pain.

Disclosures: **P. Cho:** None. **J. Lim:** None. **S. Lee:** None. **Y. Kang:** None. **S. Oh:** None. **S. Jung:** None.

Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

Location: Hall A

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Topic: D.08. Pain

Support: Matrix Biology Institute (USA)

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Title: Modulation of TRPV1 channels by sodium hyaluronate

Authors: *E. DE LA PEÑA GARCIA[1], R. CAIRES[1], E. LUIS[1], F. J. TABERNER[2], G. FERNANDEZ-BALLESTER[2], A. FERRER-MONTIEL[2], E. A. BALAZS[3], A. GOMIS[1], C. BELMONTE[1];
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Abstract: TRPV1 channels of nociceptor endings play a critical role in peripheral pain transduction and are considered the final integrators of noxious stimuli. Ostearthritis (OA) is a joint pathology accompanied by intense pain. Nociceptive nerve endings of the joint synovial membrane are normally exposed to high molecular weight sodium hyaluronate (HMW-HA) contained the synovial fluid. HA appears degraded and diluted in painful OA whereas intra-articular injection of HMW-HA (viscosupplementation) reduces pain. We studied whether such pain reduction is mediated through a modulation by HA of the TRPV1 channels present in joint nociceptive terminals. Measurement of intracellular calcium changes (FURA-2AM), and patch-clamp recordings in several configurations were carried out in HEK-293 cells transfected with TRPV1-EYFP, and in cultured DRG neurons responsive to heat, capsaicin and low pH. In both HEK-TRPV1-EYFP and DRG neurons, exposure to HA decreased significantly the amplitude of the [Ca2+]i elevations evoked by these stimuli. Whole-cell membrane currents in HEK-TRPV1-EYFP and firing discharges recorded in cell-attached configuration in DRG neurons evoked by capsaicin, were also significantly reduced by exposure to HA. Single-channel recordings in HEK-TRPV1-EYFP evidenced that the inhibitory effect resulted from a decrease in the opening probability of TRPV1 channels. Intra-articular injection of HA in rats reduced significantly the frequency of nerve impulse discharges evoked by intra-arterial injection of capsaicin. Also, intra-plantar injection of HA in mouse significantly shortened the latency of nocifensive responses to heat (hot plate test). “In silico” docking analysis showed a high probability for an electrostatic-type interaction between HA and a short sequence “H+xRG” located in the extracellular S5-pore helix loop of the TRPV1 channel. Mutation (TRPV1 K615A/R617A) produced a channel whose current density was not significantly reduced by HA. Altogether, these findings suggest that HA inhibits TRPV1 channels in nociceptors, thereby explaining its analgesic effects in osteoarthritis. All experimental procedures were carried out according to Spanish Royal Decree 1201/2005 and the ECC directive 2010/63/EU.

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Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 602.03/M1

Topic: D.08. Pain

Title: Spontaneous L-glutamate release enhancement and outward current produced by thymol in adult rat spinal substantia gelatinosa neurons

Authors: C. WANG, Z.-H. XU, T. FUJITA, C.-Y. JIANG, L. ZHU, T. YU, R. HIRAO, *E. KUMAMOTO;
Dept Physiol, Saga Med. Sch., Saga, Japan

Abstract: Thymol, which is contained in thyme essential oil, has various actions including antinociception, nerve conduction inhibition and transient receptor potential (TRP) channel activation. It has not yet been examined how thymol affects synaptic transmission. Although TRP channels expressed in the peripheral and central terminals of primary-afferent neuron are involved in nociceptive transmission, the central compared to peripheral terminal TRP channels have not yet been fully examined in property. In order to know whether thymol modulates excitatory transmission with a focus on TRP activation, we investigated its effect on glutamatergic spontaneous excitatory transmission in spinal cord lamina II (substantia gelatinosa; SG) neurons which play a pivotal role in modulating nociceptive transmission from the periphery. The experiment was performed by applying the conventional blind whole-cell patch-clamp technique to the SG neurons of adult rat spinal cord slices. Superfusing thymol (1 mM) for 3 min increased the frequency of spontaneous excitatory postsynaptic current (sEPSC) with a minimal increase in its amplitude in all neurons examined. Seventy-eight % of the neurons also produced an outward current at a holding potential of -70 mV. The sEPSC frequency increase and outward current produced by thymol were concentration-dependent with almost the same half-maximal effective concentration values of 0.18 and 0.15 mM, respectively. These activities of thymol (1 mM) were repeated at a time interval of 30 min, although sEPSC frequency increase in the second application had a tendency to be smaller in extent than that of the first one while the peak amplitudes of the outward currents in the first and second applications were almost the same. Thus, the presynaptic effect but not outward current recovered with a slow time

course after washout of thymol. A voltage-gated Na^+-channel blocker tetrodotoxin did not affect the thymol activities. The sEPSC frequency increase was inhibited by a TRPA1 antagonist HC-030031 but not a TRPV1 antagonist capsazepine, while these antagonists had no effect on the outward current. These results indicate that thymol increases the spontaneous release of L-glutamate onto SG neurons by activating TRPA1 channels while producing an outward current in SG neurons without TRPA1 and TRPV1 activation. These actions of thymol were similar in TRPA1 activation and outward current production to those of its stereoisomer carvacrol which is different in the position of -OH in the benzene ring from thymol. Thymol activities revealed in the present study could contribute to at least a part of its antinociceptive effect.

Disclosures: **C. Wang:** None. **Z. Xu:** None. **T. Fujita:** None. **C. Jiang:** None. **L. Zhu:** None. **T. Yu:** None. **R. Hirao:** None. **E. Kumamoto:** None.

Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 602.04/M2

Topic: D.08. Pain

Support: KAKENHI 23700470

Title: Carvone presynaptically enhances glutamatergic spontaneous excitatory transmission by activating TRP channels in the adult rat spinal substantia gelatinosa

Authors: Q. KANG, *T. FUJITA, C.-Y. JIANG, L. ZHU, C. WANG, T. YU, R. HIRAO, E. KUMAMOTO;
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Abstract: Transient receptor potential (TRP) channels in the spinal dorsal horn lamina II (substantia gelatinosa; SG), which are involved in the modulation of nociceptive transmission, have not yet been thoroughly examined in property. Various plant-derived chemicals including capsaicin, allyl isothiocyanate and menthol activate the TRP channels, resulting in an increase in the spontaneous release of L-glutamate onto SG neurons in spinal cord slices. The property of the TRP channels has been investigated in the cell body of primary-afferent neuron and in heterologous cells expressing the channels. We have recently reported that eugenol and zingerone, which activate TRPV1 channels in the cell body of primary-afferent neuron, activate TRPA1 channels in the SG. 1,8-Cineole, which is well-known to be a TRPM8 agonist, activated TRPA1 channels in the SG, while its stereoisomer 1,4-cineole activated TRPV1 channels. As a

result, we have proposed the idea that TRP channels located in the cell body and central terminal of primary-afferent neuron may differ in property from each other. A monoterpene ketone (-)-carvone, which is contained in spearmint oil, has been reported to activate TRPV1 channels expressed in dorsal root ganglion (DRG) neurons. In order to know a detail of the property of the central terminal TRP channel, we examined the effects of (-)-carvone and its stereoisomer (+)-carvone, which is contained in caraway oil, on glutamatergic spontaneous excitatory transmission by applying the conventional blind whole-cell patch-clamp technique to SG neurons of adult rat spinal cord slices. (-)-Carvone and (+)-carvone increased the frequency of spontaneous excitatory postsynaptic current (sEPSC) in a reversible and concentration-dependent manner with a small increase in its amplitude. This increase in sEPSC frequency was accompanied by a small inward current. Half-maximal effective concentrations of (-)-carvone and (+)-carvone in increasing sEPSC frequency were 0.70 mM and 0.72 mM, respectively. The (-)-carvone but not (+)-carvone activity was inhibited by a TRPV1 antagonist capsazepine. On the other hand, the (+)-carvone but not (-)-carvone activity was inhibited by a TRPA1 antagonist HC-030031. These results indicate that (-)-carvone and (+)-carvone activate TRPV1 and TRPA1 channels, respectively, resulting in an increase in spontaneous L-glutamate release onto SG neurons, with almost the same efficacy. Such a difference in TRP activation between the stereoisomers of carvone as well as cineole may serve to know the property of TRP channels located in the central terminal of DRG neuron in the SG.

Disclosures: **Q. Kang:** None. **T. Fujita:** None. **C. Jiang:** None. **L. Zhu:** None. **C. Wang:** None. **T. Yu:** None. **R. Hirao:** None. **E. Kumamoto:** None.

Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

Location: Hall A

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Program#/Poster#: 602.05/M3

Topic: D.08. Pain

Support: Neurosurgery Pain Research Institute, Johns Hopkins School of Medicine

Title: Loss of function in trpv3 associated with olmsted syndrome and erythromelalgia

Authors: Z. PANG, Z. LI, *M. J. CATERINA;
Neurosurg., Johns Hopkins Sch. Med., Baltimore, MD

Abstract: Olmsted Syndrome (OS) is a rare human skin disorder characterized by dramatic dermatological and sensory abnormalities. Patients with OS develop multilating palmoplantar

keratoderma and periorificial keratotic plaques, as well as severe pain and itch sensation. Recently, OS has been linked to mutations in the non-selective ion channel Transient Receptor Potential Vanilloid 3 (TRPV3), which is specifically expressed in skin keratinocytes. Several TRPV3 mutations identified in OS patients (Gly573Ser, Gly573Cys, Trp692Gly) as well as their mouse homologues have been shown to be constitutively active and to cause cell death when transfected into HEK293 cells. It remains unclear how the changes of this ion channel in the skin lead to sensory abnormalities, especially the pain phenotype in OS patients. Existing mouse lines carrying these TRPV3 mutations (Gly573Ser, Gly573Cys) have been described as models of Atopic Dermatitis with itch. However, so far there is no mouse model of OS with a pain phenotype resembling that of human patients. In 2014, several new TRPV3 mutations (Leu673Phe, Gly568Cys) were reported in OS patients with erythromelalgia, a condition associated with extreme pain and dramatic vasoreactivity. in the present study, we sought to figure out the functional roles of these mutations, by transfecting them into HEK293 cells and monitoring their effects on cell survival, cytosolic calcium and whole cell current. Mutation TRPV3 Gly568Cys caused dramatic cell death while TRPV3 Leu673Phe had no effect on cell survival. Upon stimulation with the TRPV3 agonist 2-APB, cells expressing the TRPV3 Leu673Phe mutant channel exhibited little calcium influx, while those expressing TRPV3 Gly568Cys showed robust calcium influx. In whole cell patch-clamp recordings, TRPV3 Leu673Phe showed no constitutive activity and could not be activated by 2-APB. However, TRPV3 Gly568Cys demonstrated constitutive activity and a further elevation of current with 2-APB stimulation. Our work provides evidence that both gain-of-function and loss-of-function TRPV3 mutations might contribute to the development of OS with erythromelalgia.

Disclosures: **Z. Pang:** None. **Z. Li:** None. **M.J. Caterina:** F. Consulting Fees (e.g., advisory boards); Hydra Biosciences SAB Member.

Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

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Topic: D.08. Pain

Support: NIH Grant NS055159

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New Jersey Health Foundation

Title: Calcium influx through TRPV1 inhibits mechanosensitive Piezo channels via phosphoinositide depletion

Authors: *T. ROHACS, I. BORBIRO, D. BADHEKA;
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Abstract: Piezo2 channels mediate rapidly adapting mechanically activated currents in sensory dorsal root ganglion (DRG) neurons. Expression of these mechanosensitive ion channels in a subset of TRPV1 positive neurons suggests their role in pain related sensory mechanotransduction. We show that capsaicin application inhibited rapidly adapting mechanically activated currents in TRPV1 positive DRG neurons. TRPV1 activation also inhibited heterologously expressed Piezo1 and Piezo2 ion channels in whole-cell patch clamp experiments. Inclusion of the plasma membrane phospholipid phosphatidylinositol 4,5-bisphosphate [PI(4,5)P2] or its precursor PI(4)P in the patch pipette alleviated this inhibitory effect. Activation of PLCβ by stimulating muscarinic receptors only marginally inhibited mechanically activated Piezo1 currents. Experiments using phosphoinositide sensors revealed that activation of PLCδ by a robust calcium influx through TRPV1 severely depleted PI(4,5)P2 and PI(4)P. On the other hand, muscarinic stimulation of PLCβ significantly decreased PI(4,5)P2 levels, but only induced a small decrease of PI(4)P. This differential activation of PLC isoforms may explain the difference between the inhibitory effects of these two PLC pathways. Depletion of PI(4,5)P2 and PI(4)P using a chemically inducible lipid phosphatase replicated the inhibition of Piezo1 currents. Additionally, PI(4,5)P2 and PI(4)P applied to excised inside-out patches inhibited the rundown of Piezo1 activity further emphasizing the significance of these phosphoinositides in Piezo channel regulation. Here we demonstrate that the activity of Piezo channels require the presence of either PI(4,5)P2 or PI(4)P and severe depletion of both phosphoinositides by capsaicin-induced TRPV1 activation limits channel activity. This effect may contribute to the local analgesic effect of capsaicin.

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Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

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Topic: D.08. Pain

Support: Budget (Number. 8510) from Faculty of Medicine at McGill University to Sahar Jaffal.

Title: Prostaglandin E2 (through EP1 receptor) decreases the internalization of the transient receptor potential vanilloid type 1 (TRPV1) in dorsal root ganglia (DRG) neurons *in vitro* -a new mechanism in mediating the trafficking of TRPV1

Authors: *S. M. JAFFAL;
McGill Univ., Montreal, QC, Canada

Abstract: Transient receptor potential vanilloid type 1 (TRPV1) is a non-selective cation channel responsible for the pain sensation and is activated by several stimuli (including inflammatory mediators). These mediators act by increasing the availability of TRPV1 at the surface of the dorsal root ganglia (DRG) neurons and/or the activity of the channel. Prostaglandin E2 (PGE2) is a well-known inflammatory mediator that binds to one or more of its 4 receptors (EP1, EP2, EP3 and EP4) and plays a role in modulating TRPV1 and augmenting inflammatory pain. In this study, a new mechanism has been identified for PGE2-EP1 in regulating the trafficking of TRPV1 in the DRG neurons of Sprague Dawley rats. By culturing the rat DRGs, using agonists, internalization assay, collecting-quantification of the images and performing statistical analysis, the following result was found: the level of the labelled internalized TRPV1 receptor decreased, significantly, by 45% upon treating the DRGs with 50 μM of the EP1 agonist (17-Phenyl trinor prostaglandin E2, 17PGE2) compared to control groups. In contrast, no significant difference was found between the neurons that were treated with 50 μM of the EP4 agonist (prostaglandin E1 alcohol, PGE1OH) and the control ones suggesting a possible new mechanism for PGE2 (via EP1 receptor) in mediating the availability of TRPV1 at the surface of DRG neurons (and accordingly increasing inflammatory pain). Moreover, the same dose of the EP1 agonist, 17PGE2, was effective (with a similar potency to the EP4 agonist-PGE1OH) in enhancing the 10 μM capsaicin-induced cobalt influx (an efficient assay used to measure the activity of TRPV1) in the neurons indicating that decreasing the internalization of TRPV1 in the DRGs is a unique mechanism for EP1 receptor. These data are in agreement with my behavioral results, previously presented, in which the intraplantar (ipl) injection of the EP1 agonist (but not the agonists of EP2, EP3 or EP4 receptors) caused prolongation of capsaicin induced mechanical allodynia in the rats. Accordingly, identifying the exact interaction between PGE2/EP1, TRPV1, the internalization machinery & membrane cytoskeletal changes (in more details) and its impact in inflammatory pain can be of therapeutic value.

Disclosures: S.M. Jaffal: None.

Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

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SAF2014-54518-C3-1R

RYC2011-08589

Title: Acid-sensing ion channels (ASICs) detect moderate acidifications to induce ocular pain

Authors: *X. GASULL[1], G. CALLEJO[1], A. CASTELLANOS[1], M. CASTANY[2], A. GUAL[1], C. LUNA[3], M. ACOSTA[3], J. GALLAR[3], J. P. GIBLIN[1];
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Abstract: Sensory nerve fibers innervating the ocular anterior surface detect external stimuli producing innocuous and painful sensations. Protons are among the first mediators released by damaged cells during inflammation, tissue injury or other chronic ophthalmic conditions. Here, we studied whether Acid-Sensing Ion Channels (ASICs) are expressed in corneal sensory neurons from the trigeminal ganglia, their roles in the response to moderate acidifications of the ocular surface and their participation in pathologies producing ocular surface inflammation. Moderate acidic pH (6.6) activated ASIC-like currents in corneal sensory neurons, which were blocked by ASIC1 or ASIC3-specific toxins. Acidic pH depolarized corneal sensory neurons to fire action potentials, an effect blocked by the ASIC3 inhibitor APETx2. GMQ, an ASIC3 agonist, activated a population of corneal polymodal sensory nerve fibers and significantly increased the blinking and tearing rate. ASIC blockers abolished the nocifensive behaviors produced by application of either a moderate acidic stimulus or commercial ophthalmic drugs formulated in acidic solution. In a model of allergic keratoconjunctivitis, ASIC currents were enhanced and nocifensive behavior was greatly reduced by ASIC3 blockade, presumably by reducing nociceptor sensitization during the inflammatory process. In a model of dry eye disease, the role of ASICs was not as prominent. In addition to the well-established role of TRPV1, we show that ASICs play a significant role in the detection of acidic insults at the ocular surface. The identification of ASICs in corneal neurons as well as their alterations during different diseases is critical for the understanding of sensory ocular pathophysiology. They are likely to mediate some of the sensations of discomfort associated with the use of several ophthalmic

formulations and may represent novel targets for the development of new therapeutics for ocular pathologies where discomfort and pain are prominent symptoms.

Disclosures: **X. Gasull:** None. **G. Callejo:** None. **A. Castellanos:** None. **M. Castany:** None. **A. Gual:** None. **C. Luna:** None. **M. Acosta:** None. **J. Gallar:** None. **J.P. Giblin:** None.

Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

Location: Hall A

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Topic: D.08. Pain

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Title: A-kinase anchoring protein 79/150 coordinates signaling from metabotropic glutamate receptor to transient receptor potential a1 in sensory neurons

Authors: ***K. SZTEYN**[1], R. GOMEZ[1], J. DU[2], S. CARLTON[2], N. A. JESKE[1];
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Abstract: Glutamate is the dominant neurotransmitter in the nervous system and group I metabotropic receptors (mGluR1/5) are involved in peripheral inflammatory signal transduction. In the present study we identify Transient Receptor Potential A1 (TRPA1) channel as a downstream target of mGluR1/5, as dorsal root ganglia neurons (DRGs) showed significantly increased Mustard Oil (MO) currents after treatment with the specific mGluR1/5 agonist (RS)-3,5-Dihydroxyphenylglycine (DHPG). Research results indicate that this sensitization is dependent on A-Kinase Anchoring Protein 79/150 (AKAP), as neurons isolated from AKAP KO mice demonstrated no change to MO current following DHPG pre-treatment. mGluR1/5 activation has been shown to increase the activity of Protein Kinase A (PKA), a kinase anchored to multiple plasma membrane targets ins sensory neurons. We explored this notion with electrophysiological approaches, revealing WT DRG neurons to demonstrate enhanced TRPA1 activity following 8-Br-cAMP (PKA activator) treatment, whereas DRG neurons isolated from AKAP KO mice were not affected. Further, we were able to confirm electrophysiological data using nociceptive behavioral models. Pre-treatment of WT mice with 8-Br-cAMP resulted in increased nociceptive behavior in response to MO, when compared with control group. This modification of nociceptive behavior was not observed in AKAP KO littermates. In summary,

activation of mGluR1/5 in DRG neurons results in TRPA1 sensitization in an AKAP-dependent manner. Furthermore, it is probable that PKA plays a major role in this signaling paradigm.

Disclosures: **K. Szteyn:** None. **R. Gomez:** None. **J. Du:** None. **S. Carlton:** None. **N.A. Jeske:** None.

Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

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Sheila and David Fuente Neuropathic Pain Program

Title: Antinociceptive effects of CGRP8-37 recombinant peptide in a rat spinal cord injury pain model

Authors: ***C. HAN**[1], P. P. CHEN[2], S. JERGOVA[2], F. NASIRINEZHAD[3], C. COSNER[2], S. GAJAVELLI[2], J. SAGEN[2];
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Abstract: Spinal cord injury (SCI)-induced pain presents a significant clinical problem for patients with few effective long term treatments. Therefore, it is necessary to identify new therapeutic targets and approaches. Calcitonin gene related peptide (CGRP) is produced by neurons in the dorsal root ganglia and thought to play a key role in nociceptive neurotransmission in the spinal dorsal horn. Hypersensitivity to CGRP and/or sprouting in response to injury may contribute to allodynia and hyperalgesia in persistent neuropathic pain conditions. A truncated CGRP peptide, CGRP8-37, acts as a CGRP antagonist and can reverse symptoms of neuropathic and inflammatory pain in animal models.This study aims to test the analgesic potential of the neuropathic pain gene therapy candidate cDNA encoding CGRP8-37. A truncated CGRP peptide, CGRP8-37, acts as a CGRP antagonist and can reverse symptoms of neuropathic and inflammatory pain in animal models. This study aims to test the analgesic potential of the neuropathic pain gene therapy candidate cDNA encoding CGRP8-37.Human

CGRP cDNA from Open Biosystems was used to amplify analgesic CGRP8-37 sequence. The CGRP8-37fragment was subcloned downstream of the peptidylglycine-amidating monooxygenase (ssPAM/pGEMT) signal sequence to allow CGRP8-37 to be amidated and secreted, and subcloned into lenti-EGFP-WPRE viral vector. Immunocytochemical colocalization of anti-CGRP and Golgi marker anti-Giantin antibody confirmed production of secretable CGRP8-37 peptide. The recombinant lenti-sspam-CGRP8-37-EGFP virus were produced by Miami Project Viral Vector Core. Spinal cord clip compression injury was used to induce pain-related behavior in rats and tactile and cold allodynia were evaluated weekly. At 3-5 weeks post injury when pain-related behavior was clearly established, animals were injected with the lenti-sspam-CGRP8-37-EGFP or control lentivirus intraspinally into lumbar dorsal horn. Attenuation of tactile and cold allodynia was observed by 2-3 weeks post injection with gradual improvement of behavioral outcomes towards pre-injury levels by 8-9 weeks post-SCI. In contrast, allodynia persisted in animals receiving control vector. No effects on motor impairment were observed in any vector treated groups, with comparable BBB scores over the experiment duration. Our findings suggest that engineered compound constructs encoding analgesic agents have the potential to alleviate SCI-induced pain.

Disclosures: C. Han: None. **P.P. Chen:** None. **S. Jergova:** None. **F. Nasirinezhad:** None. **C. Cosner:** None. **S. Gajavelli:** None. **J. Sagen:** None.

Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

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University of Texas STARS

Title: RNA-seq based transcriptome profiling of human and mouse dorsal root ganglion yields insight into robustness of mouse models for human pain therapeutic studies

Authors: *A. TORCK, J.-Y. V. KIM, M. Q. ZHANG, G. DUSSOR, T. J. PRICE, P. RAY; The Univ. of Texas At Dallas, Dallas, TX

Abstract: The dorsal root ganglion (DRG) contains sensory neurons that innervate the surface of the body and many visceral organs. Included amongst these neurons are nociceptors, specialized neurons that detect damaging or potentially damaging stimuli, which are required for the detection of acute pain and play a key role in the development and maintenance of chronic pain states. RNA-seq has recently been used to elucidate the transcriptome of this tissue in mouse and rat but the transcriptome of human DRG has not been explored. We obtained fresh, lumbar DRG tissue from female human donors and performed 75bp paired-end polyA+ RNA-sequencing on the Illumina platform. The sequenced fragments were mapped to the Gencode v14 reference transcriptome / hg19 reference genome to yield 80M mapped fragments, and relative transcript abundance in FPKM (Fragments Per Kilobase per Million mapped fragments) was quantified using the TopHat-Cufflinks toolkit. We compared our RNA-seq dataset to publicly available mouse DRG RNA-seq data and performed integrative analysis with RNA-seq data from several tissues associated with drug side effects (e.g. heart, small intestine, whole brain) to perform an unbiased search for conserved gene expression in DRG across both species. We find that there is broad conservation of known DRG and/or nociceptor enriched genes (e.g. P2XR3, SCN10A, SCN11A, NTRK1, MRGPRD) across mouse and human DRGs. However, hierarchical clustering of gene subsets demonstrate clear divergence between mouse and human DRG in some key respects. Information theory approaches were used to identify tissue-specific genes in human and mouse DRG compared to tissues associated with drug side effects. We find strong correlation of expression across tissues between species for a few hundred DRG-specific genes, including known genes enriched in the DRG and previously unidentified ones. However, divergence in expression across tissues amongst a large subset of genes expressed in human and mouse DRG highlight differences in tissue-specific gene regulation that are likely important when considering the relevance of mouse models for development of human pain therapeutics. Ongoing efforts include adding more human DRG samples to the dataset, including samples obtained from chronic pain patients.

Disclosures: **A. Torck:** None. **J.V. Kim:** None. **M.Q. Zhang:** None. **G. Dussor:** None. **T.J. Price:** None. **P. Ray:** None.

Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

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Support: NRF Grant 2014R1A2A1A11052579

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Title: Primary afferents temporally encode the noxious stimulus for pain signaling

Authors: *K. CHO[1], J. CHOI[1], D. SIN[2], S.-P. KIM[3], D. JANG[1], S. JUNG[1];
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[3]UNIST, Ulsan, Korea, Republic of

Abstract: Even though an activation of a primary afferent C-fiber is conceptually assumed to initiate a pain response, there are studies reporting no pain response under the activation of the afferents. One of the strong explanations is the neural network that a fiber's activation is considered as a single input to central nervous system. However, the network process is not enough to interpret all the complex sensations in animal. Moreover, most primary C-fibers contain various chemoreceptors responding to each agonists. For example, TRPV1 and TRPA1 are expressed commonly on a same fiber's membrane. Thus, chemical specific processing might take an account to such a modified pain sensation. In this study, the responses and its characteristics of primary afferents for different chemicals have been investigated on *ex vivo* single fiber recording setup. The time stamps of the evoked action potentials recorded from the skin-nerve preparation from the mice were recorded. A mouse was sacrificed before each experiment, and their hind paw skin including the saphenous nerve was extracted with surgical methods. After the identification of a single fiber on the recording setup, a chemical was applied. As a result, we obtained the response for a single chemicals where the firing pattern of each showed different patterns. In every trial, the chemicals were applied on the different receptive field of the skin to prevent a counter effect from the other.

Disclosures: K. Cho: None. **J. Choi:** None. **D. Sin:** None. **S. Kim:** None. **D. Jang:** None. **S. Jung:** None.

Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

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Topic: D.08. Pain

Support: NS055159-06

Title: The role of PLCδ4 in regulation of TRPM8 channels in sensory neurons

Authors: *Y. YUDIN, T. ROHACS;
Pharmacol. and Physiol., Rutgers New Jersey Med. Sch., Newark, NJ

Abstract: The perception of ambient temperature changes is carried out by the peripheral endings of sensory dorsal root ganglion (DRG) neurons. A small population of neurons expressing the Transient Receptor Potential Melastatin 8 (TRPM8) ion channel works as a major sensor for moderately cold temperatures with a threshold of ~28°C. We and others showed that Ca^{2+} influx through recombinant TRPM8 activates a Ca^{2+} sensitive phospholipase C (PLC) isoform, which leads to depletion of phosphatidylinositol-4,5-bisphosphate with a consequent decrease in TRPM8 currents (desensitization). Previously we have found that the most abundant highly Ca^{2+} sensitive PLC isoform in DRG neurons is PLCδ4. Here we performed whole-cell patch clamp experiments on TRPM8 positive DRG neurons from PLCδ4-KO and wild-type (WT) mice. We identified two TRPM8 positive neuronal subpopulations based of their body size. Small neurons had significantly larger menthol-induced inward current densities compared to the medium-large ones. The majority of the small TRPM8 positive cells responded to the TRPV1 agonist capsaicin, while the majority of larger cells did not. In small PLCδ4-KO neurons both menthol and cold induced larger currents compared to cells from WT animals. In medium-large PLCδ4-KO cells however menthol-induced currents were similar to those in WT cells. In current-clamp experiments small neurons had a more depolarized resting membrane potential, and required smaller current injection to generate action potentials (AP) than medium-large cells. In small neurons positive current injection initially caused a train of AP during current pulses; increasing the current magnitude lead to a drastic reduction of the AP frequency in WT but KO neurons were able to generate AP at maximal frequency. In small PLCδ4-KO neurons, menthol application induced a larger depolarization and generation of AP with frequency significantly higher compared to WT neurons. Our electrophysiological experiments indicate possible differences in temperature perception between these two mouse strains. Therefore we performed behavioral experiments on PLCδ4-KO and WT mice and found higher cold sensitivity (acetone evaporation test) in KO animals. Pretreatment with the TRPM8 antagonist PBMC (10 mg/kg) reduced cold-induced responses in both groups. Our presented data support the involvement of PLCδ4 in the mechanism of regulation TRPM8 channel activity and desensitization in-vivo.

Disclosures: Y. Yudin: None. **T. Rohacs:** None.

Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

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Topic: D.08. Pain

Support: NIH Grant GM48677

Title: Functional characterization of cold-sensitive neurons using constellation pharmacology

Authors: *T. A. MEMON, R. W. TEICHERT, B. M. OLIVERA;
Dept. of Biology, Univ. of Utah, Salt Lake City, UT

Abstract: Cold-sensitive neurons comprise ~8% of the neurons within the lumbar dorsal root ganglia (DRG) of adult C57BL/6 mice. In order to study these neurons, we have employed calcium imaging, which allows us to observe functional responses from >100 cultured neurons simultaneously and to determine the signaling proteins that mediate such responses, using target-specific stimuli and subtype-selective pharmacological agents. In Teichert et al. (2012), we had reported identification of cold-sensitive neurons in DRG culture using cold bath solutions and receptor agonists such as menthol, to activate TRPM8 channels, and allyl-isothiocyanate, to activate TRPA1 channels. These neurons were then classified as cold-thermosensors and -nociceptors based on their response profiles and functional expression of various ion channels, as determined by subtype-selective pharmacological agents. With recent studies using TRPM8-/- and TRPA1-/- mice, and HEK cells overexpressing human TRPA1 channels, we have established the contribution of TRPM8 and TRPA1 channels to cold-sensation in cold-thermosensors and -nociceptors. Furthermore, we have examined the functional expression of the voltage-gated sodium channel subtypes and a broad range of potassium channels using subtype-selective pharmacological agents to comprehend the ion-channel diversity observed in cold-thermosensors and -nociceptors. As a result, we now have a better understanding of the constellations of ion channels that are functionally integrated in these neurons. Similarly, an integrated molecular picture can be determined for cold-related pain disorders such as, cold-allodynia and hyperalgesia. In the future, similar studies may elucidate how the constellations of signaling components within each cell-type change as a function of a disease state, which may ultimately help in developing novel therapies.

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Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

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Support: NIH Grant R01NS070711

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Title: Chemokine signaling mediates mechanical and cold hypersensitivity in sickle cell disease

Authors: *K. J. ZAPPIA[1], C. A. HILLERY[2,3], C. L. STUCKY[1];
[1]Cell Biology, Neurobio. and Anat., [2]Dept. of Pediatrics and Children's Res. Inst., Med. Col. of Wisconsin, Milwaukee, WI; [3]Blood Res. Inst., BloodCenter of Wisconsin, Milwaukee, WI

Abstract: Sickle cell disease (SCD) is a genetic disorder characterized by sporadic vaso-occlusive episodes that cause acute painful and debilitating crises. Beyond this acute pain, nearly 50% of adult patients with SCD also develop chronic baseline pain, and experience increased sensitivity to touch and to cold temperatures. Further, there are many reports of increased levels of inflammatory mediators in SCD. Despite the frequency and severity of the pain these patients experience, little is known about the mechanisms underlying the chronic pain and increased thermal sensitivity in SCD, or how inflammatory mediators may contribute to this phenotype. Therefore, the aim of this study is to identify mechanisms leading to mechanical and cold hypersensitivity in the Berkeley transgenic mouse model of SCD. To begin to address a possible role of inflammatory mediators, we observed that the chemokine (c-c motif) ligand 2 (CCL2) is increased in the plasma of SCD mice. CCR2, the primary receptor for CCL2, was expressed in the dorsal root ganglia of sickle and control mice at similar mRNA levels. Behavioral testing for mechanical and cold sensitivity first confirmed that sickle mice displayed both tactile hypersensitivity and enhanced cold aversion. Next, we show pretreatment with a selective CCR2 antagonist effectively alleviated the prominent behavioral mechanical hypersensitivity in sickle mice without impacting baseline sensitivity of control mice. Similarly, blockade of CCR2 significantly reduced the cold aversion in sickle mice. We have previously shown that the cold and mechanical hypersensitivity in SCD appear to be mediated, at least in part, by sensitized peripheral sensory afferents. Therefore we also report the effect of CCR2 blockade in mediating the sensitivity of isolated sensory neurons to both cold temperature and focal mechanical stimulation. The results of these studies begin to provide inside into immune regulation of hypersensitivity in sickle cell disease.

Disclosures: K.J. Zappia: None. **C.A. Hillery:** None. **C.L. Stucky:** None.

Poster

602. Peripheral Pain: Transient Receptor Potential (TRP) Receptors

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Topic: D.08. Pain

Support: NIH/NINDS R01-NS069898

Title: Distinct pathways underlying peripheral thermal and mechanical hypersensitivity induced by C-type natriuretic peptide

Authors: *A. J. SHEPHERD[1], A. TIWARI[2], L. LOO[3], D. P. MOHAPATRA[1];
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Abstract: Atrial/brain/C-type natriuretic peptides (A/B/CNP) were originally described for their role in the maintenance of blood pressure. They are also known to be involved in various vascular and inflammatory pathologies, where their release is enhanced by pro-inflammatory mediators. Prior studies have shown that activation of the A- and B-type natriuretic peptide receptors (NPR-A and NPR-B) induce bifurcation of sensory neuron central axons via activation of guanylyl cyclase (GC) and production of intracellular cyclic GMP (cGMP). Furthermore, the NPR-C receptor (originally categorized as the NP clearance receptor, due to its lack of an intracellular GC-coupling domain), is now known to couple to $G\alpha_{i/o}$-containing signaling complexes. Previous studies have shown that the $G\beta\gamma$ subunits of $G\alpha_{i/o}$-coupled NPR-C receptors can upregulate the function of transient receptor potential vanilloid-1 (TRPV1) channel via a non-canonical activation of protein kinase C (PKC) in mouse dorsal root ganglia (DRG) sensory neurons. Such modifications in TRPV1 underlie the ability of CNP to evoke thermal hyperalgesia in mice. Here we show that intraplantar CNP (100 pmol) also elicits robust and sustained peripheral mechanical hypersensitivity, which is blocked by the TRPV1 antagonist AMG9810, and attenuated by the inhibitors of $G\beta\gamma$ signaling (Gallein) and PKC (BIM-I). CNP-induced peripheral mechanical hypersensitivity was also absent in mice lacking functional TRPV1. Given that CNP also induces NPR-B-dependent cGMP production, we verified the role of cGMP-dependent protein kinase (PKG) in this phenomenon. Remarkably, co-injection of CNP with the PKG inhibitor KT5823 completely attenuated mechanical hypersensitivity, without affecting the development of thermal hypersensitivity. CNP administration also led to significant enhancement of nociceptive sensory afferent fiber density in the plantar region of mouse hind paws, and in cultured mouse DRG neurons, as well as the density of TRPV1 protein therein. Interestingly, such CNP-induced morphological changes in sensory neurons were completely attenuated by inhibition of PKG. These observations suggest that CNP released from vascular endothelia in inflamed tissue can elicit both thermal and mechanical hypersensitivity through two distinct signaling cascades: 1) NPR-C/$G\beta\gamma$/PKC-dependent modulation of TRPV1 function elicits thermal hypersensitivity, and 2) NPR-B/cGMP/PKG mediates increased neurite density, in combination with TRPV1 modulation, resulting in the development of mechanical hypersensitivity.

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Poster

603. Thalamic and Cortical Processing

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NIH Grant DE02274

Title: Impaired cholinergic modulation in the prelimbic cortex of a rat model of neuropathic pain

Authors: ***D. RADZICKI**[1], M. MARTINA[2], S. POLLEMA-MAYS[2];
[2]Physiol., [1]Northwestern Univ., Chicago, IL

Abstract: Chronic pain patients suffer from working memory deficits; similarly, chronic pain impairs animal performance on attention and memory tasks. The mechanisms underlying the attention and memory deficits remain unclear. In primates and rodents working memory and attention are encoded in the prefrontal cortex. Recent reports have shown that the prefrontal cortex and other limbic areas undergo functional and morphological reorganization in chronic pain. The medial prefrontal cortex receives extensive cholinergic input from the basal forebrain and cholinergic modulation plays a critical role in cognitive tasks such as attentional processing and working memory. We have studied the cholinergic modulation in the prelimbic (PL) medial prefrontal cortex in the Spared Nerve Injury (SNI) model of neuropathic pain. We performed patch clamp recordings from layer 5 pyramidal neurons in acute rat brain slices of the cortex contralateral to the peripheral injury and found that 1 week after surgery cholinergic modulation was severely impaired in SNI animals. The large ACh-induced leftward shift of the input/output curve observed in sham animals was almost completely abolished in SNI pyramidal neurons and acetylcholine was no longer capable of inducing the persistent firing often observed in recordings from sham animals. These changes were due to the strong reduction (~60%) of an M1-mediated muscarinic current in the pyramidal cells of SNI rats, possibly due to desensitization of the response. We suggest that the impaired cholinergic modulation in the prefrontal cortex may play a critical role in the pain-associated cognitive deficits.

Disclosures: **D. Radzicki:** None. **M. Martina:** None. **S. Pollema-Mays:** None.

Poster

603. Thalamic and Cortical Processing

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: D.08. Pain

Title: CB2 receptor activation in ventrolateral thalamus produces antinociceptive effects on a rat tail flick model

Authors: *S. RECILLAS, JR[1], I. DOTOR LÓPEZ[1], R. SÁNCHEZ-ZAVALETA[2], G. RAMÍREZ-GARCÍA[2], P. SÁNCHEZ-APARICIO[1], H. CORTÉS-CALLEJAS[3], B. FLORÁN[2]; [1]Facultad de Medicina Veterinaria y Zootecnia., Univ. Autónoma Del Estado De México., Toluca, Mexico; [2]Fisiología, Biofísica y Neurociencias, CINVESTAV-IPN, México, Mexico; [3]Lab. de Medicina Genómica, CENIAQ - INR, México, Mexico

Abstract: Peripheral CB2 receptors have been linked to immune response, inflammation and recently to nociception or allodynia. In central nervous system little is known about its expression and function of CB2 receptors in the integration of nociceptive function. CB2 mRNA has been found in thalamus but their protein expression and participation in the integration of pain signals is not known. To understand the possible effect of CB2 receptor on central nociception in the ventrolateral thalamus, we have evaluated the expression and the effect of their activation on a rat tail flick model of pain. Male Wistar rats were cannulated in the ventrolateral thalamus and microinjected with the CB2 receptor agonist JWH-133 1μM and 10μM. CB2 receptor agonist administration increases the latency to tail-flick evaluated at 15, 30, 45 and 60 minutes after administration. By immunohistochemistry we detected CB2 protein expression in neurons of the ventrolateral thalamus. This data suggested that central CB2 receptor activation can contribute to the observed antinociceptive effect of systemic administration of CB2 selective receptor agonist.

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Poster

603. Thalamic and Cortical Processing

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: D.08. Pain

Title: Activation of corticostriatal circuitry relieves acute pain

Authors: *H. Y. LIN, R. YANG, T. MANDERS, M. LEE, J. WANG;
Anesthesiol., NYU Sch. of Med., New York, NY

Abstract: Central circuits that regulate acute pain sensitivity are not well-studied. Our previous study has shown that optogenetic activation of the prefrontal cortex (PFC) produces strong anti-nociceptive effects in rats with chronic neuropathic pain and revealed that projections from the PFC to the nucleus accumbens (NAc) mediate these pain-relieving effects. However, the effect of PFC activation in acute pain states has not been demonstrated. Here, we optogenetically activate the PFC in rats with the paw incision (PI) model of acute pain, and measure the behavioral responses of this activation. Our results indicate that activation of the PFC reduces sensory symptoms of acute pain in rats, and this pain-relieving function is likely mediated by the prefrontal projections to the NAc. Furthermore, the outcome of conditioned place preference shows that PFC activation can also regulate the aversive quality of acute pain. Thus, these results indicate that the PFC can strongly influence both the sensory and affective aspects of acute pain.

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Poster

603. Thalamic and Cortical Processing

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Topic: D.08. Pain

Support: NIH Grant NS038261

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Title: Contribution of 5-HT_{2C}R to abnormal synaptic transmission in amygdala pathways in a neuropathic pain model

Authors: *W. ZHANG[1], T. A. GREEN[2], V. NEUGEBAUER[1];
[1]Pharmacol. and Neurosci., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [2]Pharmacol. and Toxicology, Univ. of Texas Med. Br., Galveston, TX

Abstract: The amygdala plays critical role in emotional-affective aspects of pain. Abnormally enhanced activity of neurons in the central nucleus (CeA) generates pain-related emotional responses and anxiety-like behaviors. CeA output can be modulated by excitatory and inhibitory synaptic inputs from the basolateral nucleus (BLA). We found impaired synaptic inhibition and increased output of CeA neurons in an arthritis pain model but underlying mechanisms remain to be determined. Serotonin receptor subtype 5-HT_{2C}R in the BLA, but not CeA, has been implicated in anxiety-like behaviors. Here we tested the hypothesis that 5-HT_{2C}R in the BLA contributes to abnormal synaptic transmission in the BLA to CeA pathway in a neuropathic pain model. Whole-cell patch-clamp recordings were made from CeA neurons in brain slices from neuropathic rats (SNL model) and from sham controls. Rats received stereotaxic injections of 5-HT_{2C}R (or control) shRNA viral vector into the BLA to knock-down 5-HT_{2C}R expression. In CeA neurons from neuropathic rats monosynaptic excitatory postsynaptic currents (EPSCs) were increased more strongly than glutamate-driven inhibitory postsynaptic currents (IPSCs), resulting in an increase of the EPSC/IPSC ratio compared to controls. In brain slices from neuropathic rats with 5-HT_{2C}R knock-down in the BLA the balance of the excitatory and inhibitory transmission onto CeA neurons was restored and the EPSC/IPSC ratio was not different from that in sham controls. The data suggest that 5-HT_{2C}R in the BLA contributes to an imbalance of excitatory and inhibitory synaptic transmission in neuropathic pain.

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Poster

603. Thalamic and Cortical Processing

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 603.05/M19

Topic: D.08. Pain

Support: NIH Grant K01AT005935

Australian Spinal Research Foundation LG2010

Title: Effect of spinal manipulation on spontaneous and evoked activity of thalamic submedius neurons

Authors: *W. R. REED, J. T. CRANSTON, S. M. ONIFER, R. S. SOZIO;
Palmer Ctr. for Chiropractic Res., Palmer Col. of Chiropractic, Davenport, IA

Abstract: Manual therapies are non-pharmacological interventions shown to be effective for treating low back pain. Their acceptance, use, and optimization have been hindered by a lack of knowledge regarding their mechanisms of action. Widespread and immediate hypoalgesia associated with spinal manipulation and other manual therapies has been attributed to alterations in central pain processing. Neurons in the thalamic nucleus submedius (Sm) respond to convergent noxious input and have large, often bilateral, receptive fields. This makes them good candidates for investigating central mechanisms of spinal manipulation. We determined the effects of simulated spinal manipulation on spontaneous and evoked extracellular activity of Sm nociceptive specific neurons in urethane-anesthetized adult male Wistar rats (n=36). Toothed forceps were attached to the L_5 spinous process and a feedback motor was used to deliver 100ms posterior-anterior manipulative thrusts (85% rat body weight). Changes in spontaneous Sm activity (impulses/s) for time intervals of 10, 30, 60, 120, and 300s before and after a control manipulation (no force) or spinal manipulation protocol were determined (see Table). Neural responses to 10s of noxious mechanical stimulus (tail pinch, 795g arterial clip) were also recorded. Baseline activity (10s immediately prior to noxious stimulus) was subtracted from the 10s evoked response. Changes in evoked Sm activity due to the noxious tail pinch and spinal manipulation are shown in the Table. There appeared to be a small increase of mean spontaneous Sm activity following spinal manipulation at durations of 30, 60 and 120s compared to the control manipulation. Spinal manipulation appeared to result in a decrease in mean evoked response to noxious tail pinch compared to control manipulation. Further statistical analyses are being performed. A significant decrease in evoked noxious response following spinal manipulation could be involved with the immediate hypoalgesia shown clinically to occur.

Spontaneous Activity Intervals	Manipulation Control Mean change impulse/s (SD)	Spinal Manipulation Mean change impulse/s (SD)
10s	0.04 (1.7)	0.02 (1.5)
30s	0.1 (1.6)	0.32 (1.5)
60s	0.18 (1.4)	0.23 (1.2)
120s	0.15 (1.2)	0.22 (1.3)
300s	0.31 (1.5)	0.0 (1.1)
Evoked Activity Tail Pinch	0.13 (6.7)	-0.55 (4.2)

Disclosures: **W.R. Reed:** None. **J.T. Cranston:** None. **S.M. Onifer:** None. **R.S. Sozio:** None.

Poster

603. Thalamic and Cortical Processing

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 603.06/M20

Topic: D.08. Pain

Support: NIH Grant NS038261

NIH Grant NS081121

Title: SK channel function in the amygdala in arthritis pain - behavioral evidence

Authors: ***J. THOMPSON**, G. JI, V. NEUGEBAUER;
Pharmacol. and Neurosci., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Persistent pain is an important healthcare issue with significant emotional and affective consequences. Here we focus on beneficial effects of activating small-conductance calcium-activated potassium (SK) channels in the amygdala, a brain center of emotions that plays an important role in central pain modulation and processing. SK channels have been reported to regulate neuronal activity in the central amygdala (CeA, output nucleus) but not lateral nucleus of the amygdala. We tested the effects of riluzole, a clinically available drug for the treatment of amyotrophic lateral sclerosis. Actions of riluzole include activation of SK channels. Evidence in the literature suggests that riluzole may have antinociceptive effects through an action in the brain but not the spinal cord. Here we test the hypothesis that riluzole inhibits pain behaviors by acting on SK channels in the CeA in an arthritis pain model. Systemic (i.p.) application of riluzole inhibited audible (nocifensive response) and ultrasonic (averse affective response) vocalizations of arthritic rats (6 h postinduction of a kaolin-carrageenan monoarthritis in the knee) but did not affect spinal withdrawal thresholds, which is consistent with a supraspinal action. Stereotaxic administration of riluzole into the CeA by microdialysis also inhibited vocalizations, confirming the CeA as a site of action of riluzole. Stereotaxic administration of a selective SK channel blocker (apamin) into the CeA had no effect by itself but inhibited the effect of systemic riluzole on vocalizations. In contrast, stereotaxic application of a selective blocker of large-conductance calcium-activated potassium (BK) channels (charybdotoxin) into the CeA did not affect the inhibitory effects of riluzole. Off-site administration of apamin into the basolateral amygdala (BLA) as a placement control also did not block the effects of riluzole. The results suggest that riluzole can inhibit supraspinally

organized pain behaviors in an arthritis model and these beneficial effects are mediated specifically by SK channels in the CeA, but not BLA, and not by BK channels.

Disclosures: **J. Thompson:** None. **G. Ji:** None. **V. Neugebauer:** None.

Poster

603. Thalamic and Cortical Processing

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 603.07/M21

Topic: D.08. Pain

Support: Boston Scientific Grant

Title: Pain increases cortical power and enhances cortico-cortico coupling

Authors: ***B. W. LEBLANC**, P. BOWARY, C. Y. SAAB;
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Abstract: Our lab has previously demonstrated that pain enhances power in the electrocorticographic (ECoG) signal recorded over primary somatosensory (S1) cortex during awake resting states in the rat. The first aim of our current study was to validate an increase in S1 power following pain and, second, to show altered signal coherence between S1 and prefrontal cortex (PFC) using a less-invasive electroencephalographic (EEG) approach. EEG recordings were obtained above S1 and PFC under resting conditions. Power spectral density (PSD) within 3-30 Hz was computed using fast Fourier transform (250 Hz sampling rates, FFT size 256) using Spike 2 (CED). Two pain models were used: Acute pain by intradermal capsaicin injection in the hindpaw; chronic pain by chronic constriction injury (CCI) of the sciatic nerve. In the capsaicin model, PSD increased by 15% in S1 contralateral to capsaicin injection and increased by 18% in PFC (n=6 rats, $p<0.05$). In addition, coherence between PFC and S1 increased by 15% (n=6 rats, $p<0.05$). In the chronic model, 7 days after CCI PSD in S1 was increased by 29%, PSD in PFC was increased by 54%, and coherence between PFC and S1 increased by 15%) (n=6 rats, $p<0.05$) Our results validate our previous EcoG findings using more clinically relevant EEG recordings. Moreover, our data suggest that pain enhances cortico-cortico coupling and that PFC power potentially discriminates between acute and chronic pain.

Disclosures: **B.W. LeBlanc:** None. **P. Bowary:** None. **C.Y. Saab:** None.

Poster

603. Thalamic and Cortical Processing

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Topic: D.08. Pain

Support: NIH Grant NS038261

NIH Grant NS081121

Title: SK channel function in the amygdala in neuropathic pain - electrophysiological evidence

Authors: *V. A. YAKHNITSA, J. THOMPSON, V. NEUGEBAUER;
Pharmacol. and Neurosci., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: The amygdala plays a key role in the regulation of the emotional-affective component of pain. Increased activity of amygdala output neurons in the central nucleus (CeA) account for emotional responses and anxiety-like behavior in different pain models. Therefore, control of abnormal amygdala activity would be a useful strategy in pain and associated emotional disorders. Small-conductance calcium-activated potassium (SK) channels are emerging as therapeutic targets for a number of disorders. SK channels have been implicated in the neuroprotective effects of riluzole, a clinically available compound for the treatment of ALS. Here we test the hypothesis that riluzole can mitigate pain-related changes of CeA neurons in a rat model of neuropathic pain. Whole-cell voltage- and current-clamp recordings were made from latero-capsular CeA neurons in brain slices from normal/sham rats (controls) and from neuropathic rats 3-4 weeks after spinal nerve ligation (SNL). Neuropathic rats had developed mechanical hypersensitivity and anxiety-like behavior by the time brain slices were obtained. CeA neurons recorded in brain slices from SNL rats showed increased excitability measured as the number of spikes in response to depolarizing current injections compared to neurons from control rats. Riluzole decreased spiking in brain slices from control and neuropathic rats. Coapplication of a selective NMDA receptor antagonist (AP5) did not reduce the inhibitory effects of riluzole. Riluzole had no effect on the apamin-sensitive medium afterhyperpolarization (mAHP) evoked in CeA neurons from control rats. CeA neurons in brain slices from neuropathic rats lacked an apamin-sensitive mAHP but riluzole was able to restore the AHP. The results suggest that riluzole inhibits abnormal neuronal discharges of amygdala output neurons by activating SK channels and restoring the mAHP in a neuropathic pain model.

Disclosures: V.A. Yakhnitsa: None. **J. Thompson:** None. **V. Neugebauer:** None.

Poster

603. Thalamic and Cortical Processing

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 603.09/M23

Topic: D.08. Pain

Support: NIH-GM1026911

Title: Single unit responses to acute pain stimulus in the acc and s1 in awake rats

Authors: *T. R. MANDERS, A. S. TONG, Q. ZHANG, Z. CHEN, J. WANG;
Anesthesiol., New York Univ., New York, NY

Abstract: Pain is a complex, multidimensional experience involving the activation of a number of brain regions. Two of these regions _ the primary somatosensory cortex (S1) and the anterior cingulate cortex (ACC) _ have been well demonstrated to play roles in pain processing. Whereas S1 is thought to be important in the sensory-discriminative aspect of the pain experience, the ACC is thought to be important for the affective-motivational experience of pain. We performed extracellular recordings in both regions in awake, behaving rats using tetrode array microdrives during acute pain episodes. After isolating well-separated units from the spiking activity, we characterized the unique properties of these important regions' responses to acute pain. We found that both the S1 and ACC responded to the acute, noxious stimulus, but the response properties are distinct. Between these regions, we found differences in the percentage of units responding, the duration and the direction of the responses (increase or decrease).

Disclosures: T.R. Manders: None. **A.S. Tong:** None. **Q. Zhang:** None. **Z. Chen:** None. **J. Wang:** None.

Poster

603. Thalamic and Cortical Processing

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 603.10/M24

Topic: D.08. Pain

Title: Neurons in the transitional zone (TZ) in rat sensorimotor cortex play an important role in modulating pain processing in the contralateral TZ

Authors: *R. S. WATERS[1], A. L. DE JONGH CURRY[2], O. V. FAVOROV[3];
[1]Dept. of Anat. and Neurobio., Univ. Tennessee Hlth. Sci. Ctr., Memphis, TN; [2]Biomed. Engin., Univ. of Memphis, Memphis, TN; [3]Biomed. Engin., Univ. of North Carolina, Chapel Hill, Chapel Hill, NC

Abstract: Introduction: We previously reported that neurons in the transitional zone (TZ) in rat sensorimotor cortex respond to contralateral nociceptive input. Inactivation of TZ by local cooling or lidocaine injection lowers pain sensibility in the contralateral limb as measured by performance on a water bath foot withdrawal task. Inactivation of TZ by localized injection of lidocaine applied to the cortical surface or by injection into physiologically identified sites in the depths of TZ also reduced pain sensibility in the ipsilateral limb. This finding raised the possibility that TZ may be modulating pain sensibility in the opposite TZ, in part, through an interhemispheric pathway. Following lidocaine injection into TZ, the balance of excitation and inhibition in the opposite TZ most likely becomes transiently disrupted leading to the elevated pain threshold. Methods: Rats were anesthetized with 2.5% isoflurane. The skull was opened to expose sensorimotor cortex, and SI was mapped with microelectrodes to identify a region lying adjacent to the forepaw and hindpaw representations that was minimally responsive to non-noxious stimulation but responded to thermonoxious stimulation. Thermonoxious stimulation, designed to activate C-nociceptor afferents, was applied by lowering the hindlimb in a 47°-48° C heated water bath for a maximum of 15 sec. TZ was inactivated by microinjection of lidocaine into layer V of TZ. Interhemispheric connections between TZ were examined using intercortical microstimulation. Electrolytic lesions were used to mark recording sites. At the end of experiments, rats were perfused, brains were blocked, and hemispheres were flattened and cut tangentially to reveal the barrel field. Results: 1. Thermonoxious stimulation applied to a hindlimb activated neurons in the contralateral TZ. 2. An interhemispheric connection exists between TZ in both hemispheres. 3. Lidocaine injection into TZ lowered pain sensibility in both contralateral and ipsilateral hindlimbs. 4. Pain sensibility was reversed more rapidly in the ipsilateral hindlimb compared to the contralateral hindlimb. 5. Even in cases where pain sensibility was not reversed in the contralateral hindlimb, it was always reversed in the ipsilateral hindlimb. Conclusion: Interhemispheric connections between TZ very likely serve to modulate homotopic sites in the opposite TZ. One role of this modulation is to regulate pain sensibility in the ipsilateral limb.

Disclosures: R.S. Waters: None. **A.L. De Jongh Curry:** None. **O.V. Favorov:** None.

Poster

603. Thalamic and Cortical Processing

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Program#/Poster#: 603.11/M25

Topic: D.08. Pain

Support: NINDS Grant NS13742

Title: Role of Cav3.1 T-type Ca^{2+} channel in trigeminal neuropathic pain

Authors: *E. YU, S. CHOI, R. R. LLINÁS;
Dept. of Neurosci & Physiol, New York Univ. Sch. of Med., New York, NY

Abstract: Trigeminal neuropathic pain (TNP) is considered one of the most severe pain syndromes in human experience. Thus, management of TNP has attracted much attention over the years, especially as it is often unresponsive to the existing medical treatments. In this study, we investigate possible mechanism that may underlie pain processing, using an animal model of TNP. Pain was induced by partial ligations of infraorbital nerve (IoN). A clear mechanical allodynia was observed in all animals two weeks following surgery. In all cases allodynia was accompanied by an increment of a low frequency band EEG activity. This modification in brain activity, lead us to consider the possibility that sensory processing change in thalamocortical network could be responsible for this abnormal function, and most particularly, the presence of a thalamocortical dysfunction. Using voltage sensitive dye imaging (VSDI), in thalamocortical slice of TNP induced animal brain, we found, clear loss of lateral inhibition in the somatosensory cortex, following 40 Hz stimulation. This loss of lateral inhibition, we determined, correlates well the augmented peripheral pain in IoN territory after TNP induction. By contrast to deafferentation in normal animals, lateral inhibition found to be retained on the brain slice of TNP induced Cav3.1 T-type Ca2+ channel KO mice, which also showed no evidence of neuropathic pain. The findings thus suggest, that the presence of Cav3.1 T-type Ca2+ channels is one of the crucial elements in chronic pain processing in our model. Thus, modifications in ionic channel properties in thalamocortical network can result in pathophysiological conditions that alter sensory or motor properties leading to functional abnormality. Although the contribution of hyper excitability of peripheral sensory neurons to chronic neuropathic pain is not questioned, the abnormally augmented activity of central nervous system indicate the presence of a central neuropathic mechanism in accordance with the thalamocortical dysrhythmia syndrome hypothesis.

Disclosures: E. Yu: None. **S. Choi:** None. **R.R. Llinás:** None.

Poster

603. Thalamic and Cortical Processing

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: D.08. Pain

Support: NIH Grant NS038261

NIH Grant NS081121

Title: Contribution of 5-HT_{2C}R to CRF1 receptor activation in amygdala neurons in a neuropathic pain model

Authors: ***G. JI**[1], T. A. GREEN[2], V. NEUGEBAUER[1];
[1]Pharmacol. and Neurosci., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [2]Pharmacol. and Toxicology, Univ. of Texas Med. Br., Galveston, TX

Abstract: The amygdala plays a key role in emotional-affective aspects of pain and in pain modulation. Evidence suggests that serotonin receptor subtype 5-HT_{2C}R in the amygdala (basolateral nucleus, BLA) contributes to anxiogenic behavior and anxiety disorders. Previous studies from our group and others showed that the central nucleus (CeA) serves major amygdala output functions to generate emotional-affective behaviors and also modulate nocifensive responses. CeA output can be modulated by excitatory and inhibitory inputs from the BLA. Our studies showed that corticotropin releasing factor CRF1 receptor plays a key role in amygdala plasticity in arthritis pain and in the reciprocal relationship between pain and anxiety. The role of CRF1 in neuropathic pain and mechanisms of activation of the amygdala CRF system remain to be determined. Here we addressed the hypothesis that 5-HT_{2C}R in the BLA drives CRF1 activation to increase CeA activity in neuropathic pain. Extracellular single-unit recordings were made from CeA neurons in anesthetized neuropathic rats (SNL model) and in sham controls. Background activity and evoked responses of CeA neurons were increased in neuropathic rats compared to sham controls. Activation of 5-HT_{2C}R in the BLA by stereotaxic application of WAY-161503 increased the responses of CeA neurons in neuropathic rats and this effect was blocked by co-administration of a CRF1 receptor antagonist (NBI27914), implicating CRF1 receptors in the facilitatory effects of 5-HT_{2C}R on amygdala output. Local (BLA) knockdown of 5-HT_{2C}R with stereotaxic injections of 5-HT_{2C}R shRNA viral vector eliminated the inhibitory effect of NBI27914 on the responses of CeA neurons in neuropathic rats. The data suggest that 5-HT_{2C}R in the BLA contributes to neuropathic pain-related amygdala activity through a mechanism that involves activation of CRF1 receptors.

Disclosures: G. Ji: None. **T.A. Green:** None. **V. Neugebauer:** None.

Poster

603. Thalamic and Cortical Processing

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 603.13/M27

Topic: D.08. Pain

Title: Thalamic interneurons may play a role in altered mechanical thresholds following subthalamic deep brain stimulation in Parkinsonian rats

Authors: *L. GEE[1], A. RAMIREZ-ZAMORA[3], D. SHIN[2], J. G. PILITSIS[4];
[1]Albany Med. Col., Greenwich, NY; [2]Albany Med. Col., Center for Neuroscience and Neuropharmacology, NY; [3]Dept. of Neurol., [4]Dept. of Neurosurg., Albany Med. Ctr., Albany, NY

Abstract: Nigrostriatal degeneration in Parkinson's disease (PD) results in motor and non-motor symptoms. Chronic pain is reported in 65-80% of patients and clinical studies show altered nociceptive responses in PD patients, which may be modulated by subthalamic deep brain stimulation (STN DBS). Others have shown altered nociceptive responses in several rodent models of PD. Here, we explore the mechanism of how STN DBS could alter firing frequency in the ventroposteriolateral (VPL) thalamus in a rodent model of PD. We use the right medial forebrain bundle 6-hydroxydopamine (6OHDA) lesion model of PD. Sham rats received saline injections. Rats were tested behaviorally for mechanical thresholds using vonFrey filaments from 1.0g to 26.0g, during high (HF, 150Hz) and low (LF, 50Hz) frequency STN DBS and off stimulation. We also recorded single unit recordings in the VPL during mechanical stimuli application during and off STN DBS. Cells with receptive fields were found in the left hind paw using gentle brushing. VonFrey filaments of different weights (0.6g, 4.0g and 15.0g) were then applied to the left hind paw during and off HF and LF STN DBS. Behaviorally, mechanical thresholds are increased significantly by STN DBS at both HF and LF in parkinsonian rats ($p=0.004$, $p=0.005$ respectively) but not sham rats ($p>0.05$). Single unit recordings revealed two distinct waveforms in the VPL, which we believe to be relay and interneuron cells. In PD rats, interneurons displayed higher firing rates than in shams in response to the 4.0g ($p=0.034$) and 15.0g ($p=0.007$) fibers. Furthermore, firing frequency increased from 0.6 to 4.0g ($p<0.02$) and 4.0g to 15.0g ($p<0.01$) in parkinsonian rat interneurons, but not in sham interneurons. On HFS, interneuron and relay cell firing frequency may decrease in parkinsonian rats, while interneurons increase in shams. On LFS, interneuron firing frequency may decrease, while relay cell activity increases in parkinsonian rats. We are the first to show that STN DBS increases mechanical thresholds in parkinsonian rats. Furthermore, we hypothesize that STN DBS influences the VPL indirectly to alter sensory processing coming from the periphery by changing firing rates and patterns in both interneurons and relay cells during their response to nociceptive stimuli. Currently, our results are limited by a small sample size, however future experiments will focus on determining whether the VPL plays a significant role in the mechanism by which STN DBS alters mechanical thresholds.

Disclosures: **L. Gee:** None. **A. Ramirez-Zamora:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Boston Scientific. F. Consulting Fees (e.g., advisory boards); TEVA neuroscience. **D. Shin:** None. **J.G. Pilitsis:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH 1R01CA166379. F. Consulting Fees (e.g., advisory boards); Medtronic, Boston Scientific, St. Jude.

Poster

603. Thalamic and Cortical Processing

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: D.08. Pain

Support: KIST intramural funding 2E25210

Title: Role of posterior thalamic nuclei in formalin induced nociception of awake behaving mice

Authors: ***Y. HUH**, J. CHO;
Korea Inst. of Sci. and Technol., Seoul, Korea, Republic of

Abstract: Posterior thalamic nuclei (Po), higher order thalamic structure, receive inputs from the spinal cord, brainstem, and layer5 of the cortex and send output to various parts of the cortex. It has been hypothesized to have roles in somatosensory information processing as part of a paralemniscal pathway and have been implicated to be associated with pathological pain. Neurons in the Po have been shown to increase firing rate in headache and spinal cord injury (SCI) animal models under anesthesia. However, how they respond to repeated inflammatory nociception has not yet been investigated. In this study we investigated whether neurons in the Po progressively increase activity to repeated inflammatory nociception induced by formalin in awake behaving mice. Total of three formalin injections were given with 4 week term between injections to allow time for recovery. Changes in behavioral nociceptive responses to successive formalin injections were first analyzed and then neuronal responses to each injection were analyzed. Results showed that successive exposure to formalin induced greater behavioral nociceptive responses. Neuronal activities in the Po, in contrast, decreased relative to the baseline with successive formalin injections. Discrepant Po neuronal activity changes in our study may be due to different roles in processing pain information; role of Po in processing

greater inflammatory nociception may be different from the role of Po in processing headache or hyperalgesia associated with SCI. It may also be due to differences in arousal state, since our study was done in the awake behaving state while other studies were done under anesthesia. Overall, our study suggest that decreased firing rate of neurons in the Po may actually lead to increased inflammatory nociceptive responses.

Disclosures: Y. Huh: None. **J. Cho:** None.

Poster

603. Thalamic and Cortical Processing

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Topic: D.08. Pain

Support: NIH Grant NS038261

NIH Grant NS081121

Title: SK channel function in the amygdala in neuropathic pain - behavioral evidence

Authors: *V. NEUGEBAUER, G. JI, J. THOMPSON;
Pharmacol. and Neurosci., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Neuropathic pain is a serious healthcare problem. Treatment strategies are limited and often have variable efficacy and serious side effects. Neuropathic pain is associated with negative affective states, anxiety and depression. The amygdala plays a key role in the emotional-affective dimension of pain. Here we focused on small-conductance calcium-activated potassium (SK) channels in the amygdala to control pain behaviors. We tested the beneficial effects of riluzole, which is a clinically available drug for the treatment of amyotrophic lateral sclerosis. Riluzole has a number of actions, including activation of SK channels. Some evidence in the literature suggests that riluzole may have antinociceptive effects in neuropathic pain through a supraspinal site of action. We hypothesized that riluzole can inhibit pain behaviors by acting on SK channels in the amygdala output nucleus (CeA) in rat model of neuropathic pain. Supraspinally organized audible (nocifensive response) and ultrasonic (emotional-affective response) vocalizations and spinal reflex thresholds were measured in normal/sham rats (controls) and in neuropathic rats 4 weeks after spinal nerve ligation (SNL). Neuropathic rats showed increased vocalizations and mechanical hypersensitivity. The experimental strategy was to apply riluzole systemically (i.p.) and block SK channels in the amygdala pharmacologically to

determine their involvement in the predicted beneficial effects of riluzole. Systemic application of riluzole inhibited audible and ultrasonic vocalizations, but not spinal reflexes, of neuropathic rats when ACSF was administered stereotaxically into the amygdala (CeA) as vehicle control. In contrast, riluzole had no effect when a selective SK channel blocker (apamin) was administered stereotaxically into the CeA, indicating that SK channels in the CeA mediate the inhibitory effects of riluzole. Off-site administration of apamin into the lateral-basolateral amygdala area as a placement control did not block the inhibitory effects of riluzole. The results suggest that riluzole has beneficial effects on pain behaviors in a model of neuropathic pain that are mediated at least in part by SK channels in the CeA.

Disclosures: V. Neugebauer: None. **G. Ji:** None. **J. Thompson:** None.

Poster

603. Thalamic and Cortical Processing

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: D.08. Pain

Support: NINDS Grant NS13742

Title: Pathophysiological implication of CaV3.1 T-type Ca^{2+} channel in trigeminal neuropathic pain

Authors: *S. CHOI, E. YU, R. R. LLINÁS;
Dept. of Neurosci & Physiol, New York Univ. Sch. of Med., New York, NY

Abstract: The perturbation of normal sensory processing, by internally generated low-frequency brain rhythm, is one of the crucial pathophysiological issues concerning chronic neuropathic pain. To explore the molecular mechanisms responsible for such low-frequency rhythmicity related neuropathic pain, we investigated thalamocortical rhythms in mice lacking CaV3.1 T-type Ca2+ channel (knock-out, KO). Our results determined that such animals show a dramatic attenuation of mechanical allodynia in trigeminal neuropathic pain. Thus, following infraorbital nerve ligations, KO mice demonstrated a significantly reduced of the delta rhythm (1-4 Hz) in primary somatosensory (S1) cortex and its interconnected thalamic nucleus (VPM, ventroposteriomedial), compared to the increased delta rhythm in littermate control mice (wild-type, WT). In addition, the thalamocortical peak frequency rhythm shift, from theta (4-8 Hz) to delta presented in WT, was not observed in CaV3.1 KO mice. The S1-VPM coherence was also higher in theta band of CaV3.1 KO compared to WT. These results indicate the pivotal role of

thalamic CaV3.1 T-type Ca2+ channels in the alteration of thalamocortical rhythm and its functional connectivity in TNP, indicating that central neuropathic pain must be considered as a thalamocortical dysrhythmia. Our results offer clear implications concerning new understanding the pathophysiological mechanisms supporting neuropathic pain and take us one more step closer to develop more effective therapeutic approaches.

Disclosures: S. Choi: None. **E. Yu:** None. **R.R. Llinás:** None.

Poster

603. Thalamic and Cortical Processing

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 603.17/M31

Topic: D.08. Pain

Title: Evidence of thalamocortical dysrhythmia in patients with fibromyalgia

Authors: *G. RABELLO, K. WALTON, J. DELFINO, R. LLINÁS;
Ctr. for Neuromagnetism, New York Univ. Sch. of Med., New York, NY

Abstract: Fibromyalgia (FMS) is a chronic pain condition that occurs in 1 in 73 adults in the United States, amounting to around 5 million people. Fibromyalgia Syndrome is characterized by widespread musculoskeletal pain that can be set off by “tender trigger points” in muscle groups throughout the body. Fibromyalgia occurs more often in women (3.4% of women, 0.5% of men), and the prevalence raises sharply in middle age, to a maximum of 7.4% in the 70-79-year age group (Lawrence et. al., 2008). There are no universally accepted best practice guidelines for FMS treatment, mostly because the underlying cause of the pain is not well understood (Clauw, 2009). Methods: MEG recordings of spontaneous activity were made from 22 patients (women, age 27-62) meeting the American College of Rheumatology Criteria for FMS (Wolfe et. al., 2010) using a 275 channel (CTF) instrument. Recordings compared patients suffering from pain with healthy adults (15 women, age 23-64). We performed spectral analysis using the Welch method and independent component analysis (ICA) on the sensor data. Components were localized before and after band pass filtering in the delta-theta, alpha, beta and gamma bands using a recursive weighted minimum norm algorithm. Preliminary Results: MEG recordings from patients suffering from pain showed increased low rhythm activity characterized by peaks in the delta and/or theta ranges. Mean spectral energy (MSE) is positively correlated to the Fibromyalgia Impact Questionaire (FIQ) in the delta, theta, beta and gamma ranges. Source localizations showed increased low frequency activity in the postcentral cortex, orbitofrontal cortex, thalamus and cingulate gyrus in patients. Discussion: Our preliminary findings indicate

that constant low frequency oscillations are present in patients, and their strength is correlated to the severity of FMS. Localizations further corroborate the hypothesis that this abnormal activity is characteristic of thalamocortical dysrhythmia (TCD) (Llinas et. al., 1996). Thus, preliminary results strongly indicate that the mechanism of persistent neuropathic pain entails a resonant interaction between thalamus and cortex. References: 1. Lawrence, Reva C., et al. "Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part II." Arthritis & Rheumatism 58.1 (2008): 26-35. . 2. Clauw DJ, Am J Med 122, S3-S13 (2009). 3. R. R. Llinas, U. Ribary, D. Jeanmonod, E. Kronberg, P. P. Mitra, Proc Natl Sci U S A 96, 15222 (1999).

Disclosures: **G. Rabello:** None. **K. Walton:** None. **J. Delfino:** None. **R. Llinás:** None.

Poster

603. Thalamic and Cortical Processing

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 603.18/M32

Topic: D.08. Pain

Support: NIH NIDCR Grant 1R01DE022129

Title: Nociception related gene expression in the lateral thalamic region during the estrous cycle

Authors: *M. UMORIN, C. JOHNSON, L. L. BELLINGER, P. R. KRAMER;
Biomed. Sci., Texas A&M Univ. Baylor Col. of Dent., Dallas, TX

Abstract: The affect hormonal changes have on central nervous system orofacial mechanisms are largely unknown. Nociception signals can be modulated as they pass through the thalamus and ascend to other brain regions. We hypothesize that sex differences in nociception result, in part, by alterations in central nociception processing, particularly the thalamus. To address this hypothesis all known cDNAs were screened (large gene screen) in the caudalis, pariaqueductal gray, lateral thalamus, cingulate cortex and somatosensory cortex of 250g female Sprague-Dawley rats. Significant changes in gene expression were observed in each brain region, but in the thalamic region a cluster of several gabergic genes showed reduced expression during late proestrus, early estrus as based on vaginal smears. This is a time during the estrous cycle of reduced orofacial nociception. These gene array studies were followed by real-time PCR and ELISA analysis. Estradiol levels were also measured by RIAs. Our results indicate that both RNA and protein expression of vgat, GAD1, GAD2, GABARAPL1 was significantly reduced in the lateral thalamic area when plasma estradiol levels were elevated(i.e. late proestrus, early

estrus). GAD1 and GAD2 are enzymes in GABA production, vgat transports GABA into vesicles and GABRAPL1 functions in GABA receptors signaling. The results are consistent with the idea that during the estrous cycle, when estradiol is elevated, GABAergic signaling in the lateral thalamic region is diminished which can modulate nociception signaling to other regions of the brain such as the somatosensory cortex. Future experiments will test how modulating thalamic gabergic signaling affects orofacial nociception in females.

Disclosures: M. Umorin: None. **C. Johnson:** None. **L.L. Bellinger:** None. **P.R. Kramer:** None.

Poster

603. Thalamic and Cortical Processing

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Topic: D.08. Pain

Support: NIH Grant NS038261

NIH Grant NS081121

Title: mGluR5 and endocannabinoids interact at the amygdala-prefrontal cortical synapse to increase pyramidal cell output in a pain model

Authors: *T. KIRITOSHI, V. NEUGEBAUER;
Pharmacol. and Neurosci., Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Medial prefrontal cortex (mPFC) and amygdala interact and undergo neuroplastic changes in pain states. Our previous studies showed that pain-related decreased pyramidal cell activity is causally linked to increased BLA output and that co-activation of metabotropic glutamate receptor 5 (mGluR5) and cannabinoid receptor CB1 in the mPFC restores pyramidal cell output in a pain model. However, synaptic and cellular mechanisms are not fully understood and the role of BLA input to the mPFC remains to be determined. Here we used optogenetic techniques to test the hypothesis that restoring impaired mGluR5-driven endocannabinoid signaling at the BLA-mPFC synapse removes abnormally enhanced feedforward inhibition and increases pyramidal output in an arthritis pain model. Brain slices containing the mPFC were obtained from rats that received stereotaxic injections of rAAV5/CaMKIIa-hChR2(H134R)-eYFP into the BLA to selectively express channel rhodopsin 2 (ChR2) on axons of BLA pyramidal cells. Whole-cell voltage- and current-clamp recordings were made from visually

identified pyramidal cells in layer V of the infralimbic mPFC in brain slices from normal and arthritic rats (5-6 h after intraarticular injections of kaolin and carrageenan into one knee). Laser light stimulation of ChR2-expressing BLA axons evoked monosynaptic EPSCs (short onset latency, small onset jitter, preserved by TTX+4-AP and blocked by AP5+CNQX) and polysynaptic IPSCs (long onset latency, large onset jitter, abolished by TTX+4-AP and blocked by NBQX or bicuculline). A positive allosteric modulator for mGluR5 (VU0360172) increased light-activated synaptically evoked spiking (E-S coupling) in mPFC pyramidal cells under normal conditions through a mechanism that involved endocannabinoid signaling but failed to do so in the arthritis pain model. Co-application of VU0360172 with a CB1 agonist (ACEA) decreased BLA-driven feedforward inhibition to increase E-S coupling. The results suggest that pyramidal cells in the mPFC receive monosynaptic excitatory inputs and feedforward synaptic inhibition from the BLA and that interaction of mGluR5 and endocannabinoids in this pathway can restore pyramidal cell output in a pain model.

Disclosures: **T. Kiritoshi:** None. **V. Neugebauer:** None.

Poster

603. Thalamic and Cortical Processing

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Topic: D.08. Pain

Support: NIH Grant NS-069847

NIH Grant NS-079687

Title: Thalamic trigeminovascular neurons have preferential sensitivity to different colors of light: implications for photophobia during migraine

Authors: *R. NOSEDA, R. SAAVEDRA-WALKER, R.-R. NIR, A. MELO-CARRILLO, R. BURSTEIN;
Anesthesia, Beth Israel Med. Ctr/ Harvard Med. Sch., Boston, MA

Abstract: Exacerbation of migraine headache by light (photophobia) is a disabling neurological symptom experienced by most migraineurs with normal eyesight. To date, there is some information on selective sensitivity to blue light among blind migraineurs with partial light perception, and no data on whether migraine-type photophobia may be color-selective in migraine patients with normal eyesight. While testing color-sensitivity in migraineurs, we also

attempted to determine whether dura/light-sensitive thalamo-cortical neurons (implicated recently in photophobia) respond preferentially to different colors of light and whether their response preference depends on their location in the thalamus. To answer these questions, we used a calibrated LED-based light stimulator and *in vivo* multi-unit electrophysiological recording to sample a large number of dura-sensitive and dura-insensitive thalamic neurons in the rat. We found that stimulation with blue light evoked the strongest activation of dura-sensitive neurons in the lateral posterior (LP) and posterior (Po) thalamic nuclei as compared to white light. Green light induced a mild increase in neuronal firing in LP and Po. Red light, however, did not induce any significant change of baseline activity in neither of the thalamic nuclei recorded. In the ventral posteromedial thalamic nucleus no significant increase was observed with any color of light. Our findings suggest that photoactivation of dura/light-sensitive thalamic neurons is dependent on the relative contribution of retinal photoreceptors, which can explain why some colors of light may be more painful than others during migraine.

Disclosures: **R. Noseda:** None. **R. Saavedra-Walker:** None. **R. Nir:** None. **A. Melo-Carrillo:** None. **R. Burstein:** None.

Poster

604. Pain Physiology

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Topic: D.08. Pain

Support: Chinese NSF 31171065

Chinese NSF Key Grant 30530260

Title: Upregulation of Ih expressed in IB4-negative Aδ nociceptive DRG neurons contributes to mechanical hypersensitivity associated with cervical radiculopathic pain

Authors: *D. LIU;
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Abstract: Some patients with cervical radiculopathy develop severe pain, which can be extremely difficult to treat and severely limit patients' daily functions. Cervical radiculopathic pain (CRP) often associates with aberrant mechanical hypersensitivity. Primary sensory neuron's ability to sense mechanical force forms mechanotransduction. However, whether this property undergoes activity-dependent plastic changes and underlies mechanical hypersensitivity

associated with CRP are poorly understood. Here we present a new CRP model producing a chronic and stable mechanical compression of C7/C8 dorsal root ganglia (DRG) in rats, which induces dramatic behavioral mechanical hypersensitivity that mimics the pain symptoms observed clinically. Following chronic compression of C7/C8 DRGs, isolectin-B4 (IB4) negative Aδ-type (IB4- Aδ) nociceptive DRG neurons, but not IB4-positive (IB4+) or IB4- C-type nociceptive neurons exhibited frequent spontaneous activity together with hyperexcitability. Focal mechanical stimulation on somata of IB4- Aδ neurons mimicking movements of the neck elicited exaggerated high-frequency firing and long-lasting afterdischarge, indicative of abnormal neuronal mechanical hypersensitivity. Quantitative analysis of hyperpolarization-activated cation current (Ih) revealed that Ih was greatly upregulated in IB4- Aδ neurons, but not in either IB4+ or IB4- C neurons from CRP rats. Mechanistic studies by pharmacological tools indicated that increased Ih on IB4- Aδ neurons underlies the spontaneous activity together with neuronal mechanical hypersensitivity, which further contributes to the behavioral mechanical hypersensitivity associated with CRP. This study sheds new light on the functional plasticity of a specific subset of nociceptive DRG neurons, namely IB4- Aδ neurons to mechanical stimulation and reveals a novel mechanism that could underlie the mechanical hypersensitivity associated with CRP

Disclosures: D. Liu: None.

Poster

604. Pain Physiology

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Topic: D.08. Pain

Support: NIH Grant NS065926

University of Texas STARS

Title: Bioinformatic analysis of angiotensin ii receptor type 2 expression in the dorsal root ganglion

Authors: *A. SHY[1], D. C. SESSIONS[2], J.-Y. KIM[1], T. HOLEMAN[1], D. V. TILLU[3], T. J. PRICE[3];
[1]Pharmacol., Univ. of Arizona, Tucson, AZ; [2]Physics, New Mexico Inst. of Mining and Technol., Socorro, NM; [3]Sch. of Behavioral and Brain Sci., Univ. of Texas, Dallas, TX

Abstract: Mechanisms and targets of neuropathic pain remain elusive. The search for them often requires knowledge of anatomical expression of potential pharmacological targets for the treatment of neuropathic pain. Recently, a highly specific angiotensin II type 2 receptor (AT2) antagonist showed efficacy as a treatment for postherpetic neuralgia in clinical trials. A potential mechanism, based largely on preclinical studies, was attributed to the presence of AT2 in nociceptive neurons of the dorsal root ganglion (DRG). However, anatomical expression of AT2 in the DRG had been detected by low-throughput antibody techniques and the specificity of these antibodies has been questioned. We investigated the anatomical expression of AT2 using MATLAB analysis of five Gene Expression Omnibus (GEO) datasets containing microarray expression for normal male and female human tissue and normal mouse tissue from several strains. We also investigated the anatomical expression of AT2 in normal female DRG using RNA Seq. In this high-throughput bioinformatic analysis, we found virtually no AT2 expression in DRG in either normal mouse or human tissue. Additionally, we found virtually no AT2 expression in human TG, human spinal cord, or mouse spinal cord. The conspicuous lack of AT2 expression in DRG and sensory tissues necessitates further examination of the proposed mechanisms by which putative AT2 antagonists may modulate nociceptive transmission.

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Poster

604. Pain Physiology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 604.03/M37

Topic: D.08. Pain

Title: IB4 expressing, but not TRPV1 expressing nociceptive fibers mediate movement-evoked breakthrough cancer pain

Authors: K. CARLSON[1], I. PELLETIER[1], J. HAVELIN[1], I. IMBERT[1], F. PORRECA[2], *T. E. KING[1];
[1]Biomed. Sci., Univ. of New England, Biddeford, ME; [2]Univ. of Arizona, Tucson, AZ

Abstract: Cancer-induced bone pain is characterized by persistent, ongoing pain, with many patients also reporting breakthrough (BT) pain. BT pain is defined as transient episodes of severe to excruciating pain that “breaks through” medication (i.e., opioids) controlling ongoing pain. In

patients with bone metastases, voluntary (e.g., switching positions in bed) or involuntary (e.g., cough) movements can trigger BT pain that is severe and requires immediate, fast-acting opioid medications. Pain that "breaks through" medication controlled ongoing pain suggests that mechanisms mediating ongoing and BT pain may be distinct. We demonstrate that movement of the tumor bearing hindlimb produces conditioned place aversion (CPA), indicating that this treatment induces increased pain. Such observations are consistent with reports of BT pain in patients with metastases within the bone. Further, movement-induced CPA breaks through morphine administration that is sufficient to block ongoing pain, a key aspect of BT cancer pain within the clinical setting. Using this novel measure we examined the hypothesis that BT pain is mediated by IB4 expressing, non-peptidergic nociceptive fibers, but not TRPV1 expressing, primarily peptidergic nociceptive fibers. Ablation of TRPV1 expressing fibers failed to block movement-induced CPA. In contrast, ablation of IB4 expressing fibers blocks movement-induced CPA. These data indicate that IB4 expressing, non-peptidergic nociceptive sensory fibers mediate BT cancer bone pain whereas TRPV1 expressing, primarily peptidergic nociceptive sensory fibers do not. Acknowledgements: This work was supported in part by an NIH COBRE grant P20GM103643 and a grant from the Maine Cancer Foundation.

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Poster

604. Pain Physiology

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Topic: D.08. Pain

Title: Tamoxifen-inducible nav1.7 KO mouse: characterization at an RNA, protein and electrophysiological level

Authors: *L. DENG, R. M. REESE, S. D. SHIELDS, K. SCEARCE-LEVIE, D. H. HACKOS; Neurosci. Dept., Genentech Inc., South San Francisco, CA

Abstract: The sodium channel Nav1.7 is an attractive pain target based on human genetic evidence. Gain-of-function mutations in Nav1.7 are associated with inherited severe pain conditions, such as inherited erythromelalgia (IEM) or paroxysmal extreme pain disorder (PEPD), whereas individuals carrying loss-of-function mutations are congenitally insensitive to pain (CIP). Although the role of Nav1.7 in pain perception has been extensively studied, it is still not fully understood how loss of Nav1.7 results in such a severe insensitivity to pain and whether

removal of Nav1.7 in the adult would lead to the same phenotype. In an attempt to answer these questions, we employed a tamoxifen-inducible Nav1.7 cKO mouse (pCAGG-CreERT$^{tg/-}$ x scn9a$^{loxP/loxP}$). Upon intraperitoneal dosing of tamoxifen, Nav1.7 RNA is rapidly removed from the DRG and is undetectable by qPCR within 1-3 days after the final of three tamoxifen doses. In contrast, Nav1.7 protein levels within the DRG decay more slowly with a half-life of approximately 1 week, becoming undetectable by 6-8 weeks. To examine the electrophysiological properties of DRG neurons lacking Nav1.7, we cultured DRG neurons isolated from either Nav1.7 cKO mice or wildtype littermates that had been previously dosed with tamoxifen (8 week timepoint). We employed the Nav1.7-selective scorpion toxin OD1 and the Nav1.7-selective spider toxin ProTx-II to demonstrate the loss of Nav1.7 in DRG neurons from Nav1.7 cKO mice. Further voltage-clamp recordings allowed us to determine the consequences of removal of Nav1.7 on the surface expression of other Nav and Cav channels. Finally, current-clamp recordings allowed us to determine the effects of removal of Nav1.7 on the excitability of different classes of DRG neurons.

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Poster

604. Pain Physiology

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Topic: D.08. Pain

Support: Finnish Academy grant 277442 to RG.

Title: Purinergic signaling in trigeminal nociceptive system in meninges and trigeminal ganglia

Authors: *C. GUERRERO-TORO[1,2], G. YEGUTKIN[3], R. GINIATULLINA[1,2], K. KOROLEVA[2], E. KILINC[2], R. GINIATULLIN[1,2];
[1]Neurobio., Univ. of Eastern Finland, Kuopio, Finland; [2]A. I. Virtanen Inst., Kuopio, Finland; [3]Univ. of Turku, Turku, Finland

Abstract: ATP and its degradation products like ADP and adenosine are efficient signaling molecules in the nociceptive system. Previously we suggested a potential role of ATP in migraine pathophysiology (Giniatullin et al., 2008). However, the sources and stability of ATP in meningeal tissues and the role of its degradation products controlled by NTPDases were little studied. In this project, we combined Ca2+ imaging, purine biochemical assays, NTPDase

staining and electrophysiological methods to explore the role of various purines in rat trigeminal ganglion cell cultures and isolated meninges obtained from young and adult Wistar rats. We found a very low nanomolar level of extracellular ATP and ADP in meninges whereas the concentrations of AMP and adenosine were about two orders higher indicating high efficiency of enzymes designed for inactivation of ATP and ADP. Accordingly, both ATP and ADP were able to generated large Ca2+ transients in isolated trigeminal neurons and surrounding satellite cells (satellite glial cells and fibroblasts). Consistent with purinergic hypothesis of migraine, the key migraine mediator neuropeptide CGRP significantly increased the level of extracellular ATP measured with luciferase biochemical assay or explored with the lead nitrate staining. However, CGRP did not change the rate of ATP degradation. The main source of extracellular ATP appeared to be meningeal vessels as indicated by staining of phosphate groups. To test the pro-nociceptive activity of purines in meningeal tissues we used the extracellular recordings of nociceptive firing in hemiskull preparation (Shatillo et al., 2013). We found that ATP is the most effective inducer of nociceptive firing whereas the similar effect of ADP did reach a significant level. In contrast, AMP and adenosine were almost ineffective in meningeal nerves. Our data suggest efficient CGRP-sensitive signaling via extracellular purines in the trigeminal nociceptive system, primarily mediated by ATP. Giniatullin R, Nistri A, Fabbretti E. (2008). Mol Neurobiol., 37:83-90. Shatillo et al., (2013). Neuroscience, 253:341-9.

Disclosures: C. Guerrero-toro: None. **G. Yegutkin:** None. **R. Giniatullina:** None. **K. Koroleva:** None. **E. Kilinc:** None. **R. Giniatullin:** None.

Poster

604. Pain Physiology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 604.06/M40

Topic: D.08. Pain

Title: Modulation of pain transmission in the dorsal horn circuit: from ionic channels to information transfer of noxious inputs

Authors: P. SACRÉ[1], Y. GUAN[2], W. S. ANDERSON[3], *S. V. SARMA[1];
[1]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [2]Anesthesiol. and Critical Care Med., [3]Neurosurg., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Chronic pain affects about 100 million American adults---more than the total affected by heart disease, cancer, and diabetes combined. Despite their great need, neuropharmacology and neurostimulation therapies for chronic pain have been associated with suboptimal efficacy

and limited long-term success as their mechanisms of action are unclear. Understanding the mechanisms of pain transmission to predict its modulation by therapies is therefore essential toward pain management, yet current mechanistic models suffer from several limitations. Among others, they are not amenable to tractable mathematical analysis and fail to provide a comprehensive mechanistic understanding of pain transmission. Using mathematical reduction techniques that exploit time-scale separation, we investigated the cellular dynamics in the dorsal horn circuit of the spinal cord---the first central relay of sensory (innocuous and noxious) inputs to the brain. This study proposes a reduced model of projection neurons in the dorsal horn and discusses the modulation of nociceptive information transfer to the brain. Projection neurons in the dorsal horn can exhibit a rich set of dynamics---from tonically firing to plateau potentials to endogenous bursting. Each firing pattern results in different capabilities of information transfer---from faithful transmission to enhancement to blocking of nociceptive information, respectively. The cellular firing pattern and therefore the functional capability of information transfer are driven by a dynamic balance of intrinsic properties of the neurons. A low-dimensional reduced model is sufficient to capture each firing mode. A first ultraslow variable acts as a positive feedback (ultraslow regenerative ionic channels) and is responsible for the acceleration in the depolarized state and the deceleration in the hyperpolarized state. A second ultraslow variable acts as a negative feedback (ultraslow restorative ionic channels) and is responsible for the interburst period. As a consequence, this balance of negative and positive ultraslow feedbacks plays a critical role in the modulation of pain transmission in projection neurons of the dorsal horn. The dorsal horn circuitry may also affect the capability of information transfer and the dynamics at the circuit level will remain the focus of future work.

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Poster

604. Pain Physiology

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Topic: D.08. Pain

Support: Nanoori Hospital Grant R1003401

Title: Discogenic low back pain (LBP): Is it possible for intervertebral disc (IVD) itself to generate LBP?

Authors: ***E.-H. PARK**, S.-W. MOON, H.-R. SUH, H.-C. HAN;
Physiol., Col. of Medicine, Korea Univ., Seoul-City, Korea, Republic of

Abstract: Intervertebral disc (IVD) can be a major source of low back pain (LBP). A herniated or bulging IVD which is often accompanied by degenerated IVD and spinal stenosis put stressful pressure on adjacent spinal nerves or spinal cord and the leakage of nucleus pulposus (NP) from disc tissues induce inflammatory response, thereby leading to develop chronic LBP. As another possibility, IVD themselves can generate the pain signal because it was found that sinuvertebral nerves or branches of the paravertebral sympathetic trunks (PST) innervate IVDs, and in degenerated IVDs the upregulation of neurotrophins can promote nerve fiber to grow into the deep layer of annulus fibrosus and give rise to painful IVD. However, it is not clear whether afferent fibers innervating IVDs can participate in sensory or nociceptive processing. The purpose of this study was to characterize the responses of IVD afferents in normal and punctured IVD model to intradiscal pressure. Using male SD rats (300-350g; Korea), punctured IVD model was made by puncture of IVD with 22-gauge needle followed by totally aspirating nucleus pulposus of lumbar IVDs with suction pump. *In vivo* extracellular recording of IVD afferents was done on 35 days after surgery. PST was teased into small strands and placed on a unipolar platinum electrode in warm mineral oil pool. The intradiscal pressure was controlled by the injection of saline with 5 ml syringe in a range between 100 and 3000 mmHg. Afferents activities evoked by intradiscal pressure were counted with maximum spikes per second. The firings of afferents in both normal/sham and punctured lumbar IVD were proportionally increased to the intensity of applied pressure. However, afferents in punctured lumbar IVD showed significantly increased response and significantly decreased threshold to the same pressure stimulus compared to those of normal/sham lumbar IVD. The present study implicate that the sensory information from IVDs can be transmitted to spinal cord through paravertebral sympathetic pathways, and punctured IVD model might be useful for discogenic pain study because punctured lumbar IVD apparently showed sensitized response to intradiscal pressure change than normal/sham lumbar IVD.

Disclosures: **E. Park:** None. **S. Moon:** None. **H. Suh:** None. **H. Han:** None.

Poster

604. Pain Physiology

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Topic: D.08. Pain

Support: CAPES

FAPESP 05/56663-1

Title: *In vivo* evaluation of cell activity using manganese-enhanced magnetic resonance imaging (MEMRI) in adult rats after neonatal nociceptive stimulation

Authors: *J. M. MALHEIROS[1], A. TANNÚS[2], R. GUINSBURG[3], L. COVOLAN[1];
[1]Univ. Federal De Sao Paulo, São Paulo, Brazil; [2]CIERMag-Physics Inst. of São Carlos, USP, São Carlos, Brazil; [3]Pediatrics Departament, Univ. Federal de São Paulo, São Paulo, Brazil

Abstract: Neonatal noxious stimulation in rats has been proposed to model neonatal procedural pain performed in neonatal intensive care units. Previous studies have shown that the rate of hippocampal neurogenesis as well as the behavioral repertoire of adult rats may be altered in response to neonatal noxious stimuli. Several studies have used MEMRI (Manganese-enhanced MRI) approach, since the Mn2+ can act as a marker of calcium influx into cells serving as a surrogate indicator of activated areas after stimulation. The purpose of this study is to determine, in adult animals, MEMRI signal alterations in the brain after neonatal noxious stimulation. For this, male and female rats received an intraplantar injection of CFA (complete Freund's adjuvant) on P1 (first postnatal day), P8 or P21. To assess whether nociceptive re-exposure could activate differentially the same brain areas, a subgroup of animals were also noxious-stimulated in the infancy (P1P21 and P8P21). Animals received an injection of MnCl2 (60 mg/kg) 12 hours before the new nociceptive stimulation (CFA) and 14 hours before MRI. MRI was performed on a Bruker electronic (Avance III under Paravision 5.1) adapted to a 2 Tesla superconducting magnet (Oxford Instruments 85310HR). Crossed saddle radiofrequency coil was used as a head probe for the animals, anesthetized by an i.p. injection of ketamine (95mg/kg) and xilazine (12mg/kg). The relative signal intensity was calculated as the ratio of the mean signal intensity in the region of interest (ROI) to the mean intensity of adjacent corpus callosum. Results indicate that the re-stimulated females showed higher signal intensity mainly in areas related to emotional pain control (insular cortex), recognition, learning (secondary somatosensory cortex) and pain memory (dorsal hippocampus). P1 female group showed the same signal intensity as Naïve group in areas related to pain localization (ventrolateral thalamus and primary somatosensory cortex) and showed no signal intensity alterations in the amygdala. In the dorsal hippocampal dentate gyrus, P1 females (1.551 ± 0.053 a.u.) showed higher signal intensity than P1 males (1.203 ± 0.119 a.u., $p<0.05$). This area has been recently related to associative memory. These results show that MEMRI can be used in animal models to map central nervous system areas related to processing long-term nociceptive information.

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Poster

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Topic: D.08. Pain

Support: Craig H Neilsen Foundation 257760

Title: Does macrophage migration inhibitory factor (MIF) contribute to chronic spontaneous activity in nociceptor somata after spinal cord injury?

Authors: A. BAVENCOFFE[1], Q. YANG[1], O. BLOOM[2], *E. T. WALTERS[1];
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Abstract: Chronic pain is often a permanent, severe, and poorly treated problem for people with spinal cord injury (SCI), and its mechanisms remain mysterious. In a rat model of contusive thoracic SCI we discovered that pain-related behavioral changes are associated with persistent hyperexcitability and spontaneous activity (SA) in the somata of primary nociceptors recorded *in vitro* and *in vivo* (Bedi et al. J Neurosci, 30:14870, 2010) and showed that persistent nociceptor hyperactivity plays a critical role in driving SCI pain (Wu et al. Pain, 154:2130, 2013; Yang et al. J Neurosci, 34:10765, 2014). Nociceptors have receptors for many injury- and inflammation-related cytokines and their somata are highly exposed to circulating cytokines because of the lack of an effective vascular permeability barrier in the dorsal root ganglia (DRG). Individuals with SCI show chronic elevation of several circulating pro-inflammatory cytokines, with especially high plasma concentrations of macrophage migration inhibitory factor (MIF) acutely (<2 weeks postinjury) and chronically (>1 year postinjury) after SCI (Bank et al. Arch Phys Med Rehab, 94:1498, 2015, Stein et al. Arch Phys Med Rehab, 94:1498, 2013). Importantly, MIF is reported to be necessary and sufficient for reflex hypersensitivity in nerve injury and peripheral inflammation models (Alexander et al. Exp Neurol 236:351, 2012). As a first step in testing whether circulating pro-inflammatory cytokines contribute to chronic nociceptor SA after SCI, we examined effects of MIF on excitability properties of small DRG neurons 1 day after dissociation from naive, sham-operated, or SCI rats. Extending earlier findings from naive mice (Alexander et al., 2012), we found that MIF at concentrations of 0.5-1 ng/ml (somewhat lower than measured in individuals with SCI) decreased rheobase and significantly increased SA within ~20 sec of application to nociceptors isolated from all three groups of animals. This finding supports the hypothesis that, *in vivo*, SCI-induced elevation of circulating MIF can help to drive chronic nociceptor SA. However, longer treatment with MIF (5-20 min) depolarized resting membrane potential and significantly reduced SA. While this latter result may argue against our hypothesis that MIF helps to drive somally generated SA after SCI, an alternative explanation is that our *in vitro* testing conditions enhance the responsiveness of nociceptors to prolonged exposure to MIF, causing excessive depolarization and the paradoxical decrease in excitability.

We are now exploring this possibility as well as preliminary indications that SCI produces a further increase in the responsiveness of nociceptors to MIF.

Disclosures: **A. Bavencoffe:** None. **Q. Yang:** None. **O. Bloom:** None. **E.T. Walters:** None.

Poster

604. Pain Physiology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 604.10/M44

Topic: D.08. Pain

Title: Forced exercise alleviates evoked and ongoing pain in a model of advanced, NSAID-resistant osteoarthritis

Authors: *I. IMBERT, M. WALKER, J. ALLEN, G. STEVENSON, T. KING;
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Abstract: Osteoarthritis (OA) affects an estimated 27 million adults in the US, a number likely to rise due to the aging of the population and other medical issues such as obesity. Advanced OA is often characterized by persistent, ongoing moderate to severe joint pain that is resistant to current therapies including NSAIDs. A commonly recommended non-pharmacological treatment for patients with OA pain is exercise. Clinical studies have demonstrated that aerobic and strengthening exercise can improve function and pain in patients with knee OA. In addition, a small number of studies have examined the effects of exercise on joint pathology, generally finding no benefit or exacerbation of joint pathology as determined by radiographs. The effects of forced treadmill exercise and voluntary wheel running exercise on MIA-induced joint pain were compared across 4 weeks post-injection. Rats received intra-articular monosodium iodoacetate (MIA) (4.8 mg/60 µl) or equivolume saline injection into the knee joint. Starting 10 days following MIA injection, rats in the forced exercise group were placed on a treadmill and forced to run for 30 min across 4 days starting at 12 m/min for 1 week followed by 16 m/min for the remaining weeks. Control (sedentary) rats were placed on the inactive treadmill. Rats in the voluntary exercise group were placed in cages with free access to running wheels overnight for 5 weeks prior to MIA injection to establish stable wheel running behavior. They then received intra-articular MIA or equivolume saline injections into the knee joint and were again given overnight access to the running wheels 10 days post-injection. Weight bearing on each hindlimb was measured pre-injection and weekly post-injection to assess development of weight asymmetry (D7-pre-exercise) and effects of exercise on the MIA-induced weight asymmetry (D14-D35). Treadmill exercise produced a reversal of MIA-induced weight asymmetry and

ongoing pain. Wheel running rats were divided into 2 populations, high and low running rats. MIA produces a drop in speed and distance in the high running, with the average speed at the peak 30 min dropping from approximately 30 m/min to a range of 16-20 m/min post MIA injection. Although this was in the range of the speed of the forced exercise, MIA-induced weight asymmetry remained constant across the 6 weeks post-MIA in the high runner group.
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Poster

604. Pain Physiology

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Topic: D.08. Pain

Support: CIHR MOP4918

CAPES Foundation - Brazil

Title: Effects of the natural substance (-)-alpha-Bisabolol on trigeminal central sensitisation and sensorimotor behaviour induced by acute noxious orofacial stimuli

Authors: *L. T. MELO[1,2], V. PANCHALINGAM[2], L. AVIVI-ARBER[2], P. CHERKAS[2], A. R. CAMPOS[1], B. J. SESSLE[2];
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Abstract: Our previous studies have shown that noxious orofacial stimulation including application of the inflammatory irritant mustard oil (MO) to the rat maxillary molar tooth pulp produces increased activity of medullary dorsal horn (MDH, also known as trigeminal subnucleus caudalis) nociceptive neurons reflecting trigeminal central sensitisation and increased jaw muscle electromyographic (EMG) activity reflecting nociceptive sensorimotor behaviour (eg, Chiang et al, 1998; Sunakawa et al, 1999; Narita et al, 2012). There is evidence that (−)-α-Bisabolol (BISA), a sesquiterpene alcohol presents in the essential oil from Chamomile, acts via 5-HT and TRPV1 receptors to produce anti-nociceptive and anti-inflammatory effects in animal models of acute pain. The aim of this study was to examine whether trigeminal central sensitisation and nociceptive sensorimotor behaviour evoked by orofacial noxious stimuli can be

attenuated by systemic pre-administration of BISA. In anaesthetised adult male Sprague-Dawley rats, EMG activity parameters (threshold, amplitude, duration, area under the curve) were monitored in the masseter and anterior digastric muscles in order to record the jaw-opening reflex (JOR) evoked by electrical stimulation of the tongue. In addition, the activity of functionally identified nociceptive (wide dynamic range) neurones was recorded in the MDH. The effect of BISA (30mg/kg) or vehicle (isotonic saline) on the tongue stimulation-evoked JOR or on MO-induced central sensitisation in MDH neurones was tested by intravenously administering BISA or vehicle at 10 minutes before the tongue stimulation or MO application to the maxillary molar tooth pulp. Pre-medication with BISA but not vehicle significantly reduced the JOR (N=8/group, ANOVA, post-hoc Bonferroni $p<0.05$) and it also reduced central sensitisation as reflected in its attenuation of MO-induced increases in spontaneous neuronal activity and responses to pinch/pressure (N=6/group, ANOVA, post-hoc Bonferroni $p<0.05$). These results suggest that BISA may attenuate nociceptive sensorimotor responses and central sensitisation evoked by noxious orofacial stimuli, and that this natural product may be useful clinically for the treatment of orofacial pain.

Disclosures: **L.T. Melo:** None. **V. Panchalingam:** None. **L. Avivi-Arber:** A. Employment/Salary (full or part-time):; University of Toronto. **P. Cherkas:** A. Employment/Salary (full or part-time):; University of Toronto. **A.R. Campos:** A. Employment/Salary (full or part-time):; University of Fortaleza. **B.J. Sessle:** A. Employment/Salary (full or part-time):; University of Toronto.

Poster

604. Pain Physiology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 604.12/M46

Topic: D.08. Pain

Support: Chaire de recherche du canada en neurophysiopharmacologie de la douleur chronique

Title: Selective CCR2 chemokine receptor antagonists as potential treatment of bone cancer pain

Authors: *E. MIDAVAINE, D. BARRIÈRE, J.-M. LONGPRÉ, P. SARRET;
Univ. De Sherbrooke, Sherbrooke, QC, Canada

Abstract: Many types of cancers have a propensity to metastasize to the bone microenvironment. In 75-90% of patients coping with metastatic cancer, tumor-induced bone remodeling results in moderate to severe pain, which significantly compromises the patient's

quality of life. Unfortunately, current pain relieving treatments, primarily relying on opioid analgesics, become ineffective over time and the most severe type of pain, called breakthrough pain, often remains uncontrolled. Treatments for painful osseous metastases thus require designing new therapies for improving pain control. In recent years, the CCL2/CCR2 chemokine system has gained a prominent place in the field of spinal nociceptive processing, notably in the genesis and maintenance of metastatic breast cancer-induced bone pain. Likewise, the CCL2/CCR2 axis was shown to play a central role in the bone-tumor ecosystem, establishing a fine dialogue between invasive breast carcinoma cells, infiltrating inflammatory cells, and osteoclast/osteoblast bone resident cells. The project was thus aimed at investigating the efficacy of targeting the CCL2/CCR2 axis in both acute and bone cancer pain models. First, we tested the efficacy of the CCR2 antagonist, RS 504393 (25 μg/rat, intrathecally) to alleviate mechanical allodynia in a CCL2-induced acute pain model. We observed that RS 504393 produces a significant long-duration reversal of the mechanical allodynia induced by CCL2. The breast cancer bone metastasis pain model, consisting in injecting MRMT-1 carcinoma cells (endogenously expressing CCL2/CCR2) into the female rat femoral medullary cavity, was then used to evaluate the role of CCL2 in bone pain facilitation. Cancer-induced bone destruction was observed using histological, PET and MR medical imaging. Bone matrix pathological destruction was explained by an osteoclast/osteoblast imbalance in cancer-bearing animals. In the spinal cord dorsal horn, bone cancer progression induced major glial cells activation, as observed by an increased in GFAP and Iba1 immunostainings. Moreover, pERK and pp38 stainings were observed over neuronal and glial cell population in cancer-bearing rats, respectively. CCL2 immunolabeling further revealed that CCL2 is anterogradely transported along the sciatic nerve, probably contributing to the mechanical sensitivity. Punctual spinal injection of RS 504393 significantly reduced tactile allodynia in tumor-bearing rats achieving up to 48% of pain relief. In conclusion, blocking CCL2/CCR2 axis represents a promising avenue to control bone cancer pain and improve the quality of life of patients dealing with bone metastases.

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Poster

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Topic: D.08. Pain

Support: FAPESP Grant 2013/04779-2 and 2012/11371-7

Title: The contribution of nucleus accumbens brain derived neurotrophic factor to persistent hyperalgesia development

Authors: *C. H. TAMBELI, L. CAMARGO-CALILI, E. DIAS-VIEIRA, G. G. SANTOS, C. SARTORI, C. A. PARADA;
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Abstract: Introduction - Enhanced dopaminergic activity in the nucleus accumbens (NAcc), an important component of mesolimbic system, facilitates persistent hyperalgesia development (Dias et al., 2015). Brain Derived Neurotrophic Factor (BDNF) is a neurotrophin that influences the release of dopamine in the mesolimbic dopamine system (Goggi et al., 2003). Therefore, the aim of this study was to investigate the role of NAcc BDNF in persistent hyperalgesia development. Methods - We used male Wistar rats (200-250g) and an animal model of persistent hyperalgesia in which daily subcutaneous PGE2 injection (100ng/50µl) into the rat's hind paw for 14 days induces a state of nociceptor sensitization that lasts for at least 30 days following the cessation of the PGE2 treatment. The mechanical nociceptive threshold was quantified using the paw-withdrawal test (Randall & Selitto, 1957) on days 1, 5, 7 and 14 of the persistent hyperalgesia induction and on days 1, 7, 14 and 21 after the discontinuation of the PGE2 treatment. The selective TrkB receptor agonist 7.8 Dihydroxyflavone (DHF), the selective TrkB receptor antagonist K252a or their vehicles were bilaterally administered in the NAcc during the initial 7 days of daily PGE2 treatment by two cannulae connected to osmotic mini-pumps subcutaneously implanted. The stereotaxic coordinates used were: 1.3mm anterior to Bregma; L1.7mm; V7.2mm below the skull surface. Two-way ANOVA followed by Bonferroni test was used for statistical analysis ($P<0.05$). Rats per group = 6 to 9. Results - Blockade of nucleus accumbens TrkB receptors prevented the development of persistent hyperalgesia. The mechanical nociceptive threshold of rats receiving K252a (0.016µg/µL) in the NAcc and PGE2 in the hindpaw (Mean±EPM: 112.92±3.8g) was significantly greater than that of rats receiving vehicle in the NAcc and PGE2 in the hindpaw (88.33±4g) from the 7th day of persistent hyperalgesia induction. In contrast, the activation of nucleus accumbens TrkB receptors facilitated the development of persistent hyperalgesia. In animals receiving DHF (0.83µMolar/µL) in the NAcc and PGE2 in the hindpaw the persistent hyperalgesia developed 2 days earlier and the mechanical nociceptive threshold was significantly lower (86.11±1.8g) than that of animals receiving vehicle in the NAcc and PGE2 in the hindpaw (116.11±2.5g) from the 5th day of persistent hyperalgesia induction. Conclusion - NAcc BDNF plays an essential role in the development of persistent hyperalgesia, suggesting that the action of this neurotrophin in nucleus accumbens is important for the development of chronic pain.

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Poster

604. Pain Physiology

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Topic: D.08. Pain

Support: NIH Grant HL103773

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Title: Sensitization of C-fiber nociceptors in a murine model of Sickle Cell Disease (SCD) is decreased by the inhibition of anandamide hydrolysis through local administration of URB597

Authors: *M. L. UHELSKI, K. GUPTA, D. SIMONE;
Univ. of Minnesota Twin Cities, Minneapolis, MN

Abstract: Sickle cell disease (SCD) describes a group of disorders resulting from a point mutation in the beta chain of hemoglobin. This mutation leads to the creation of sickle hemoglobin (HbS) and causes distortion of erythrocytes through polymerization under low oxygen resulting in characteristic sickle red blood cells (sRBC). Vaso-occlusion caused by accumulation of sRBCs results in ischemia-reperfusion injury, reduced oxygen supply to organs, organ damage and severe pain. Further, many patients suffer from chronic pain, including increased sensitivity to light touch and spontaneous pain. Pain may result from both inflammatory factors as well as neuropathy, which creates a complex pain syndrome that may not respond well to currently available therapies. Mouse models of SCD have been developed which expresses human hemoglobin (normal HbA or sickle HbS). Homozygous HbSS-BERK sickle mice, expressing exclusively human beta-sickle hemoglobin or HbAA-BERK control express normal human hemoglobin A were used in this study. Sickle mice develop hyperalgesia around 5 months of age, and demonstrate enhanced pain responses following hypoxia-reoxygenation. Control mice do not exhibit hyperalgesia. Since there is growing evidence that increasing local levels of endocannabinoids can decrease hyperalgesia, we examined the effect of URB597, a fatty acid amine hydrolase (FAAH) inhibitor that blocks the breakdown of the endogenous cannabinoid anandamide (AEA), on the sensitization of peripheral nociceptors in hyperalgesic sickle mice. We characterized the sensitization of C- and Aδ-fiber nociceptors in hyperalgesic sickle mice in comparison to their normal HbAA controls. In the current study administration of URB597 (10 μg in 10 μl) into the receptive field of sensitized C-fiber nociceptors significantly decreased spontaneous activity (from 0.82 ± 0.67 Hz at pre-injection to 0.19 ± 0.08 Hz at 90 min post-injection), increased mechanical response thresholds (from 5.77 ±

2.37 mN to 41.80 ± 9.16 mN at 90 min post-injection), and decreased responses evoked by 147 mN von Frey stimulation (from 105.9 ± 11.9 impulses to 13.7 ± 1.8 impulses at 90 min post-injection). These results paralleled behavioral studies in which intraplantar administration of administration of URB597 decreased mechanical hyperalgesia in HbSS mice. It is suggested that enhanced endocannabinoid activity in the periphery could alleviate chronic pain associated with SCD without undesirable side effects associated with activation of cannabinoid receptors in the CNS.

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Poster

604. Pain Physiology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 604.15/N1

Topic: D.08. Pain

Title: Mouse physiology changes over time during isoflurane anesthesia but remains within normal limits

Authors: *L. BAUER, L. LOW, C. BUSHNELL;
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Abstract: Anesthetized mice can be used in neuroimaging studies to explore neural pathways. Anesthesia can affect cerebral blood flow and oxygenation, which are important variables for functional brain imaging. Hence, it is necessary to know about the baseline physiology of mice under anesthesia. Aim: To monitor how physiological parameters change over time in mice under isoflurane and alpha chloralose anesthesia. Methods: Male C57bl/6 mice were anesthetized with either isoflurane (n=19) or alpha chloralose (n=7). Isoflurane mice were induced at 4% and maintained at 1.5-2% in a 60:40 O2:medical air mixture. Alpha chloralose-anesthetized mice were induced with 4% isoflurane, and then given an 114mg/kg i.p. injection of alpha chloralose. Breathing rate was measured using a pressure-transducer pillow; heart rate was measured with s.c. ECG leads. Core body temperature was measured with a rectal probe and maintained via an automatic temperature feedback system. Arterial blood samples were taken from a tail artery at early, mid and late time points, and pH, oxygen and carbon dioxide saturations quantified. Mice were monitored under anesthesia for up to 150 minutes. Results: Over a period of 150 minutes under isoflurane, breathing and heart rate significantly decrease ($p<0.0001$ and $p=0.036$, respectively). Core body temperature can be maintained (36.5±0.5°C). Blood pH decreases significantly over time, but does not reach the point of acidosis (pH<7.2). Also under isoflurane,

blood CO2 decreases as average respiration rate increases (p=0.133, r2=0.21). With alpha chloralose, breathing rates are lower than those of mice under isoflurane (p=.003), heart rate is below the accepted range of 450-500bpm (310-420bpm), and blood becomes acidotic (pH<7.2) over periods up to 105 minutes. Conclusions: Using isoflurane, heart rate stays within published acceptable limits of 450-500 bpm, as does blood pH (7.2-7.4), even during extended periods, but alpha chloralose causes considerable blood acidosis. There is limited information about acceptable respiration rates for an anesthetized mouse, but lower breathing rates are associated with higher blood CO2 levels, creating a potential for blood acidosis. It can be deduced that alpha chloralose does not maintain stable physiology over long periods of time, which may interfere with brain imaging results. These results suggest that mouse physiology can be effectively maintained using isoflurane in order to have a consistent baseline for blood flow to the brain, making it possible to obtain reliable results from functional brain scans which depend on blood flow and oxygenation measures.

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Poster

604. Pain Physiology

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Program#/Poster#: 604.16/N2

Topic: D.08. Pain

Support: CIHR MOP4918

Title: Effects of bacterial virulence factor applied to the rat dental pulp on nociceptive sensorimotor behaviour and medullary dorsal horn (MDH) nociceptive neurons

Authors: *V. PANCHALINGAM[1,2], V. FENG[1], L. MELO[1], L. AVIVI-ARBER[1], P. GAZERANI[2], P. CHERKAS[1], B. SESSLE[1];
[1]Fac. of Dent., Toronto, ON, Canada; [2]Hlth. Sci. and Technol., Aalborg Univ., Aalborg, Denmark

Abstract: Symptomatic irreversible pulpitis is a bacteria-induced painful inflammatory disease of the dental pulp. In an inflammatory dental pain model, we have shown that pulpal application of the inflammatory irritant mustard oil (MO) induces increased activity of medullary dorsal horn (MDH) nociceptive neurons reflecting trigeminal central sensitization and increased jaw muscle electromyographic (EMG) activity reflecting nociceptive sensorimotor behaviour (e.g. Chiang et al, 1998; Sunakawa et al, 1999; Narita et al, 2012). Given this and recent findings that

bacterial virulence factors can activate nociceptors (Chiu et al. 2013), the aim of this study was (a) to investigate whether application to the rat maxillary molar dental pulp of the gram-negative virulence factor lipopolysaccharide (LPS) or the gram-positive virulence factor lipoteichoic acid (LTA) can induce nociceptive sensorimotor behaviour and trigeminal central sensitization of MDH nociceptive neurons, and (b) compare the effects with those of MO. Electrophysiological recordings were made of bilateral masseter muscle EMG activity or the activity and responses to graded pinch of MDH wide dynamic range nociceptive neurons before (i.e., baseline) and after LPS (1mg/mL), LTA (5mg/mL), MO or vehicle (α-MEM) application to the pulp of adult male Sprague-Dawley rats (n=5-7/group) under general anaesthesia. As compared with baseline, both MO and LPS (but not LTA or vehicle) produced a significant (RM ANOVA, Tukey test, $p<0.05$) increase in EMG activity (e.g. peak amplitude, area under the curve) that began within 1 minute and lasted for 3-5 minutes. Only MO and LPS produced evidence of trigeminal central sensitization as indicated by a significantly (RM ANOVA, Tukey test, $p<0.05$) increased spontaneous activity or pinch-evoked responses of the MDH nociceptive neurons. These findings suggest that, like MO, the presence of the bacterial virulence factor LPS in the dental pulp can evoke trigeminal central sensitization and nociceptive sensorimotor behaviour and may play a role in the pain associated with symptomatic irreversible pulpitis in humans.

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Poster

604. Pain Physiology

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 604.17/N3

Topic: D.08. Pain

Title: An *in vivo* electrophysiological assay to assess blood-nerve barrier penetration in the sciatic nerve

Authors: *K.-C. CHOONG, T. M. WALL, J. L. KRAJEWSKI, X. CHI, T. E. FITCH, B. FORSTER, B. S. WILENKIN, M. J. KRAMBIS, K. M. GARDINIER, T. J. RAUB, K. RASMUSSEN, J. S. MCDERMOTT, K. K. PALMER, B. T. PRIEST, L. R. KEHN, E. S. NISENBAUM;
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Abstract: A perennial challenge in the pursuit to discover novel peripherally-restricted analgesics is determining the extent to which drugs can cross the blood-nerve barrier (BNB) to engage the intended target and modulate nociceptive signaling. While electrophysiological responses of specific primary afferent fibers have been well-characterized in teased fiber preparations, these techniques disrupt the integrity of the epineurium, precluding assessment of BNB penetration of novel compounds *in vivo*. In the current study, we develop a simple and rapid method to assess BNB penetration using multi-unit extracellular recording of the intact sciatic nerve *in vivo* in mice. Sensory afferent action potentials were recorded in the intact sciatic nerve bundle using a hook tungsten electrode following stimulation of the plantar surface of the hindpaw with a pair of fine needle electrodes. Electrically-evoked A- and c-fiber responses were identified based on their conduction velocities. The identity of c-fibers responses was further confirmed by demonstrating that longer latency discharges were initially increased for 5-10 min following intradermal injection of capsaicin (10 µl, 1%) into the hindpaw and subsequently eliminated due to desensitization of nociceptors. We subsequently validated this functional BNB penetration assay by measuring A- and c-fiber responses following systemic administration of lidocaine, a non-selective sodium channel blocker which can readily penetrate the BNB and Compound A, a Nav1.7-preferring blocker that does not appreciably cross the BNB. Results showed that both A- and c-fiber action potentials were blocked by lidocaine at unbound plasma concentrations that were also effective in a complementary *in vitro* sciatic nerve assay in which the BNB was disrupted. In contrast, systemic administration of Compound A did not affect A- or c-fiber responses despite achieving unbound plasma concentrations that were shown to preferentially suppress c-fiber responses *in vitro*, consistent with the expression of Nav1.7 on this fiber type. Moreover, local administration of compound A to the sciatic nerve based on the effective concentration observed *in vitro*, potently inhibited c-fiber responses after removal of the epineurium covering the sciatic nerve.. Collectively, these results indicate that this method can be used as a simple functional assay to measure BNB penetration of novel compounds *in vivo*.

Disclosures: **K. Choong:** A. Employment/Salary (full or part-time):; Eli Lilly & Company INC.(full time). **T.M. Wall:** A. Employment/Salary (full or part-time):; Eli Lilly & Company INC.(full time). **J.L. Krajewski:** A. Employment/Salary (full or part-time):; Eli Lilly & Company INC.(full time). **X. Chi:** A. Employment/Salary (full or part-time):; Eli Lilly & Company INC.(full time). **T.E. Fitch:** A. Employment/Salary (full or part-time):; Eli Lilly & Company INC.(full time). **B. Forster:** A. Employment/Salary (full or part-time):; Eli Lilly & Company INC.(full time). **B.S. Wilenkin:** A. Employment/Salary (full or part-time):; Eli Lilly &

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Poster

604. Pain Physiology

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Title: Functional TTX resistant sodium channels of human IPS and ES cell-derived nociceptive neurons resemble an early stage of development

Authors: *D. R. SCHMIDT[1,2], E. EBERHARDT[4], S. HAVLICEK[3], A. S. LINK[2], C. NEACSU[2], Z. KOHL[5], M. HAMPL[2,6], A. M. KIST[2], J. SCHÜTTLER[4], C. ALZHEIMER[2], J. WINKLER[5], B. NAMER[2], A. LAMPERT[2,6], B. WINNER[3];
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Abstract: The incidence of chronic pain is 20-25% worldwide, setting the research focus on revealing the basic mechanisms of pain and the development of more effective pain treatments. As human nociceptors are only rarely available, the cellular mechanisms of nociception are mostly studied in sensory neurons of rodents. Since chronic pain cannot be adequately mimicked in animal models, we took advantage of using human pluripotent stem cells (hPSC) to generate nociceptor-like neurons. Using a chemical based approach, we differentiated hPSC into human nociceptive sensory neurons that expressed BRN3A, Peripherin, TrpV1 and P2RX3, all markers of nociceptors. These stem cell derived sensory neurons showed electrophysiological properties indicative for the presence of tetrodotoxin sensitive (TTXs) and resistant (TTXr) voltage-gated sodium channels (Navs). In contrast to their counterparts from rodent dorsal root ganglia neurons, TTXr currents of hPSC-derived nociceptors unexpectedly display a significant shift of the voltage dependence of activation and fast inactivation towards more hyperpolarized potentials. The reason for this apparent discrepancy is most likely a substantial expression of the developmentally important Nav1.5 channel. In view of the limitations of animal models to recapitulate neuropathic pain, our data advances hPSC-derived nociceptors as an additionally necessary model to study developmental and pathogenetic processes underlying pain in humans and may help to develop new pain treatments.

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Poster

604. Pain Physiology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 604.19/N5

Topic: D.08. Pain

Support: KAKENHI 25293136

MEXT-SRFPU S1311009

Title: Right side specific potentiation of parabrachial-central amygdala transmission by trigeminal nerve-mediated inflammatory pain

Authors: Y. MIYAZAWA[1], M. SUGIMOTO[1], Y. TAKAHASHI[1], A. M. WATABE[1], *F. KATO[2];
[1]Dept Neurosci, Jikei Univ. Sch. Med., Tokyo, Japan; [2]Dept Neurosci, Jikei Univ., Tokyo, Japan

Abstract: Nociceptive signals arising from the superficial layer of the spinal dorsal horn (sDH) and the caudal part of the spinal nucleus of the trigeminal nerve (Sp5c) converge in the lateral parabrachial nucleus (LPB) and then are sent to the capsular part of the central amygdala (CeC). This spino-(trigemino-)parabrachio-amygdaloid pathway (Gauriau & Bernard, 2002) forms the direct route for the nociception-emotion link and shows robust potentiation in various types of pain models in rodents (Veinante et al., 2013). Lines of evidence indicate that the synaptic potentiation of the LPB-CeC transmission and increased expression of phosphorylated ERK occur exclusively in the right amygdala regardless of the side of nociception in the animal models with arthritis and formalin-induced inflammatory pain models (Guangchen & Neugebauer, 2009; Carrasquillo & Gereau, 2007). To determine whether such laterality depends on the difference in the specific mechanism in the CeC, we employed a trigeminal inflammatory pain model because, 1) unlike sDH neurons, Sp5c neurons project to bilateral LPBs, and 2) this model unexpectedly shows bilateral mechanical sensitization in the hindlimb (Sugimoto et al., 2015), which are interesting properties to compare with the spinal inflammation models. Injection of 5% formalin solution into the upper-lip of adult Wistar rats resulted in manifest face-rubbing behaviors lasting for < 1 h and bilateral mechanical sensitization in the hindlimb, where there was no injury, after 3 h. Six hours after injection, we made acute brain slices and measured LPB-CeC synaptic transmission. A marked LPB-CeC potentiation was observed in the right CeC of the orofacial formalin model regardless of the injection side. This potentiation was accompanied by decreased paired-pulse ratio and increased quantal size, suggesting changes in pre- and post-synapses characterize the functional alteration of this pathway. However, we did not find any apparent changes in NMDA/AMPA ratio in either side. These results indicate that the right amygdala plays specific primary role in regulating the strength of nociception-emotion link regardless of the location of painful sensation and inflammation at least in persistent pain lasting for several hours.

Disclosures: Y. Miyazawa: None. **M. Sugimoto:** None. **Y. Takahashi:** None. **A.M. Watabe:** None. **F. Kato:** None.

Poster

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Program#/Poster#: 604.20/N6

Topic: D.08. Pain

Support: NIH MRBS-RISE R25-GM059298

Title: Nociceptive sensitization of a defensive strike occurs centrally in Manduca sexta

Authors: *D. TABUENA, C. MOFFATT, M. FUSE;
San Francisco State Univ., San Francisco, CA

Abstract: Current preclinical models of nociception in animals such as mice or rats require multiple levels of protocol and logistical regulation. This presents an economic burden to research in the field. Here we characterize a model for hypersensitization of nociception of the defensive strike response in the insect Manduca sexta. This terrestrial caterpillar can bridge the gap between aquatic invertebrate and traditional, mammalian preclinical models. This work was based on a previous behavioral assay where a hypersensitive state was induced with a noxious stimulus. In this study, we demonstrate the ability to use M. sexta as an electrophysiological model for nociception, through development of both an *in situ* and an *in vitro* preparation. We were able to correlate nerve activity in the ventral nerve cord (VNC) with the defensive behavior and identified the afferent nerve pathway from the body wall to the VNC using mechanical stimulation with calibrated von Frey filaments and simultaneous extracellular nerve recordings, by systematically eliminated nerve projections. We then assayed both hypersensitive and non-treated animals in this manner, using a pinch as the noxious stimulus. We found that force required to induce a half maximal response in the ventral nerve cord was significantly reduced after the pinch. However, the response in afferent nerves was unchanged. The lack of significant change in afferent nerve pressure response or basal firing rate suggests that the hypersensitivity to nociception is driven by signaling factors at or after synapses in the ventral nerve cord ganglion. Furthermore, we measured changes in habituation to mechanical stimuli in a similar manner and found that habituation is attenuated peripherally but not centrally. This system provides a novel *in situ* model for studying modulation of nociception and “pain” signaling in a cheaper and less strictly regulated animal.

Disclosures: D. Tabuena: None. **C. Moffatt:** None. **M. Fuse:** None.

Poster

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Topic: D.08. Pain

Support: Grants-in-Aid and Special Coordination Funds from Kobe Gakuin University Joint Research (B)

Title: Sex differences in BDNF expression after exposure to early life stress leads to susceptibility to neuropathic pain-induced emotional dysfunction

Authors: *T. NISHINAKA, K. NAKAMOTO, S. TOKUYAMA;
Kobe Gakuin Univ., Kobe, Japan

Abstract: Early life stress leads to the pathogenesis of psychiatric disorders and chronic pain in adult patients. We have recently demonstrated that exposure to early life stress exacerbates nerve injury-induced thermal and mechanical hypersensitivity in adult male and female mice. Accumulating evidence suggests that chronic pain causes emotional dysfunction, such as anxiety and depression. The emotional dysfunction induced by persistent pain is related to functional alterations in the brain, such as frontal cortex, hippocampus and striatum. It is well known that neuronal dysfunction in these regions of the brain is also induced by early life stress. In the present study, we investigated the effect of early life stress on depression-like behavior after nerve injury in mice. In addition, we examined the expression of brain-derived neurotrophic factor (BDNF), which is known to be involved in the pathogenesis of depression. Early life stress was induced by maternal separation between 2 and 3 weeks of age combined with social isolation after weaning (MSSI). At 9 weeks of age, the sciatic nerve was partially ligated to elicit neuropathic pain. Depression-like behavior was evaluated using the forced swim test at 12 weeks of age. Tissue samples from different regions of the brain were collected at the end of maternal separation (3 weeks of age) or after the forced swim test (12 weeks of age). At 12 weeks of age, immobility time in the forced swim test was increased only in MSSI-stressed female mice with nerve injury. BDNF expression was increased in male, but not female, MSSI-stressed mice at 3 weeks of age. However, MSSI stress did not influence BDNF expression in male or female mice at 12 weeks of age. Our findings suggest that exposure to early life stress exacerbates emotional dysfunction induced by neuropathic pain in a sex-dependent manner. Changes in BDNF expression after early life stress may be associated with neuropathic pain-induced depression-like behavior in adulthood. Furthermore, sex differences in BDNF expression after exposure to early life stress may contribute to sex-specific susceptibility to neuropathic pain-induced emotional dysfunction.

Disclosures: T. Nishinaka: None. **K. Nakamoto:** None. **S. Tokuyama:** None.

Poster

604. Pain Physiology

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Topic: D.08. Pain

Title: Multi-molecular and structural profiles of the skin and cutaneous innervation that validate a pig proximal nerve injury models for translational research on human peripheral neuropathic pain

Authors: *S. B. MEILIN[1], M. DOCKUM[2], D. CASTEL[3], I. SABBAG[4], F. L. RICE[2];
[1]MD Biosci., Ness Ziona, Israel; [2]Integrated Tissue Dynamics LLC, New York, NY; [3]The Neufeld Cardiac Res. Institute, Sheba Med. Centre, Sackler Sch. of Med., Tel Aviv, Israel; [4]Lahav Res. Institute, Kibutz Lahav, Negev, Lahav, Israel

Abstract: Current therapeutics for human peripheral neuropathic pain afflictions (PNPA) typically provide at best 50% relief in less than one third of patients most of whom have debilitating side effects. A major challenge to translational research for safer, more effective therapeutics is the development and validation of cost-effective non-human models of CNPA. The pig is particularly useful especially because of comparable-to-human body size, metabolism, skin structure and innervation, as well as nerve, DRG, and spinal cord dimensions. Moreover, pigs are plentiful, relatively cheap, breed easily, have multiple offspring, and are more ethically preferable than non-human primates. We have developed a sciatic nerve trauma model performed by pre CFA-soaked loose sutures that produces hindlimb pain responses consistent with human regional CNPA such as radicular pain, sciatica, and complex regional pain syndrome. In addition to assessments of response to threshold like those tested in rodent models and humans, pigs also have complex social interactions that are negatively impacted like many in humans. In order to further validate whether this model is indeed comparable to human CNPA, we used combinations of immunomarkers for a wide variety of functionally-implicated neurochemical markers in order to compile immunocytochemical and morphological profiles of the hindleg skin and innervation as we have done previously for a variety of human CNPA, including CRPS type 1. Assessments were made on alternating sections of skin biopsies fixed by immersion in 4% paraformaldehyde as routinely done with human skin punch biopsies. Consistent with many human CNPA, the innervation of the epidermis, upper dermis and deep dermal innervation was substantially reduced with preferential preservation of sensory fibers that express calcitonin-gene-related peptide and 200kD neurofilament protein indicative of likely Aδ fibers which have been implicated in mechanical allodynia. Of particular importance, the keratinocytes of the thick multi-layered epidermis (identical to that in humans) exhibited induced alterations among a variety of normally stratified algesic and analgesic neurochemical properties like those that we have previously documented in several human CPNA including CRPS type 1.

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Poster

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Topic: D.08. Pain

Support: Danish National Research Foundation (DNRF121)

Title: Test-retest reliability of 10 Hz conditioning electrical stimulation inducing long-term potentiation-like pain facilitation in humans

Authors: ***W. XIA**, C. D. MØRCH, O. K. ANDERSEN;
Hlth. Sci. and Technolody, Aalborg Univ., Aalborg, Denmark

Abstract: Background: 10 Hz conditioning electrical stimulation (CES) has been shown to induce long-term potentiation (LTP)-like pain facilitation similar to traditional 100 Hz CES in healthy humans. The aim of the study was to assess the test-retest reliability and to estimate sample sizes required for future crossover and parallel pharmacological testing studies. Methods: Sensory changes and neurogenic inflammatory vascular reactions after 10 Hz CES to the volar forearm were assessed in 20 subjects during two identical experimental sessions separated by at least one week. Perceptual intensity ratings to single electrical stimulation at the conditioned skin site and to mechanical stimuli (pinprick and light stroking) in immediate vicinity to the conditioned skin site were recorded. Superficial blood flow and skin temperature were assessed as indicators of neurogenic inflammation. All outcome measures were assessed with 10 min intervals three times before and six times after CES. The coefficient of variation within session (CVwi) and between sessions (CVbt), and intra-class correlation within session (ICCwi) and between sessions (ICCbt) were calculated. Systematic bias was analyzed by repeated measures analysis of variance. Subsequently, the sample sizes were calculated for potential future crossover (Ncr) and parallel (Np) drug testing studies expected to detect a 30 % decrease for the individual outcome measures following 10 Hz CES. Results: For assessment of neurogenic inflammation, the superficial blood flow was found to significantly increase after CES then declined until reaching a plateau 20 minutes post CES. The blood flow showed the highest reliability (ICCwi=0.79, CVwi=3%, Ncr=3; ICCbt=0.62, CVbt=3%, Np=13) within and between 10 Hz CES sessions. Perceptual intensity ratings to light stroking (allodynia) (ICCwi=0.96, CVwi=8%, Ncr=2; ICCbt=0.89, CVbt=13%, Np=33) and pin-prick stimulation (50.1g,

secondary mechanical hyperalgesia) (ICCwi=0.9, CVwi=14%, Ncr= 6; ICCbt=0.88, CVbt =14%, Np=54) were found to significantly increase after CES and showed better reliability in crossover than parallel designs. The single electrical stimulation showed high reliability (ICCwi=0.94, CVwi=10%, Ncr=634; ICCbt=0.85, CVbt=14%, Np=11310) but with large estimated sample sizes due to a small effect by CES. Conclusion: The reliability of 10 Hz CES was acceptable in inducing LTP-like effects in the assessments of superficial blood flow, secondary mechanical hyperalgesia and allodynia in terms of sample sizes for potential crossover experimental designs.

Disclosures: **W. Xia:** None. **C.D. Mørch:** None. **O.K. Andersen:** None.

Poster

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Topic: D.08. Pain

Support: NIH Grant R01MD007807

Title: Parental modeling of stoicism and its effect on pain outcomes: Preliminary findings

Authors: *C. A. STURYCZ, B. L. KUHN, E. W. LANNON, S. T. PALIT, Y. M. GÜERECA, M. F. PAYNE, K. A. THOMPSON, J. O. SHADLOW, J. L. RHUDY;
Univ. of Tulsa, Tulsa, OK

Abstract: Past research has shown an influence of self-reported levels of stoicism on pain outcomes. Specifically, those who report higher levels of stoicism are similar to those who report low levels of stoicism in spinal nociceptive input (e.g. nociceptive flexion reflex; NFR) but differ in the report of pain sensation (e.g., pain threshold, pain tolerance). However, it is unclear if a relationship exists between parental transmission of stoicism and self-reported stoicism or pain outcomes. The current study utilized a semi-structured interview to assess attitudes about pain and history of painful experiences. One item that specifically inquired about what parents taught participants about pain was coded for the presence or absence of a stoic attitude. The relationship between this variable and self-reported stoicism (measured from fortitude, concealment, and superiority subscales of the Pain Attitudes Questionnaire, PAQ) and pain outcomes (heat, cold, ischemia, and electrocutaneous pain thresholds/tolerances). 47 healthy, pain-free participants. All statistical assumptions were tested and passed and extreme outliers were replaced using the nearest neighbor, plus one unit substitution technique. Groups did not differ on the subscales of

the PAQ (ps>.05) or NFR (ps>.05). However, those individuals taught to be stoic by their parents (n=14) had significantly higher heat pain thresholds (p<.02) and higher ischemia (p<.05), cold (p<.05), and electrocutaneous (p<.05) pain tolerances than those participants who were not taught to be stoic (n=33). Further, when PAQ subscales were entered into regression models to predict pain outcomes, the subscales were positively correlated with electric (R2=.22, p<.01), heat (R2=.18, p=.02), and cold pain tolerance (R2=.24, p<.01). These preliminary findings suggest that a family history of stoicism and trait stoicism are related to increased pain outcomes across a number of pain outcomes, primarily measures of tolerance.

Disclosures: **C.A. Sturycz:** A. Employment/Salary (full or part-time):; University of Tulsa. **B.L. Kuhn:** A. Employment/Salary (full or part-time):; University of Tulsa. **E.W. Lannon:** A. Employment/Salary (full or part-time):; University of Tulsa. **S.T. Palit:** A. Employment/Salary (full or part-time):; University of Tulsa. **Y.M. Güereca:** A. Employment/Salary (full or part-time):; University of Tulsa. **M.F. Payne:** A. Employment/Salary (full or part-time):; University of Tulsa. **K.A. Thompson:** None. **J.O. Shadlow:** A. Employment/Salary (full or part-time):; University of Tulsa. **J.L. Rhudy:** A. Employment/Salary (full or part-time):; University of Tulsa.

Poster

604. Pain Physiology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 604.25/N11

Topic: D.08. Pain

Support: Oklahoma Center for the Advancement of Science and Technology (HR12-100)

Title: The influence of placebo analgesia on pain and the nociceptive flexion reflex (NFR): Is descending inhibition engaged?

Authors: *Y. M. GUERECA, B. KUHN, S. PALIT, J. L. RHUDY;
Psychology, The Univ. of Tulsa, Tulsa, OK

Abstract: Placebo analgesia is pain reduction evoked by an inert treatment and is mediated by at least two psychological factors: expectations for pain relief and classical conditioning (e.g., pairing an inert treatment with pain reduction). Although placebo analgesia is well established, it is not clear if it influences descending inhibition of spinal nociception. Past fMRI studies suggested that supraspinal regions involved with descending modulation of pain are activated during placebo analgesia. Yet, evidence for inhibition of spinal nociception is mixed. A study

found that an expectation + conditioning (E+C) manipulation decreased dorsal horn activity. However, another study failed to show that the nociceptive flexion reflex (NFR, physiological measure of spinal nociception) was inhibited by placebo. That study used a placebo manipulation with only an expectation manipulation, and the strongest placebo effects are observed when both expectations and conditioning are manipulated. Indeed, that study also failed to show placebo effects on pain ratings. Interestingly, a recent EEG study used an E+C manipulation and found that placebo analgesia was related to cortical modulation but not spinal inhibition. Thus, the present study was designed to examine whether pain and NFR are inhibited by placebo involving E+C. 140 healthy, pain-free individuals were randomly assigned to a Natural History control group (NH, n=35), or one of three placebo manipulations: Expectation for pain relief only (E, n=35), Conditioning only (C, n=35), or Expectation + Conditioning (E+C, n=35). Suprathreshold electric stimulations were delivered to the ankle to evoke pain and the NFR before and after two sham cream applications. To induce expectation for pain reduction, the E+C and E groups were told the cream was a strong and effective painkiller (Lidocaine) whereas the NH and C groups were told it was sensor gel. However, after the first application, electric stimulus intensity was surreptitiously reduced in the E+C and C groups to include conditioning (i.e., cream paired with pain relief). Since intensity was not reduced after the second cream application, placebo analgesia was defined as the change in pain and NFR associated with the second cream application. Results show that pain was inhibited in the E+C ($p<.001$) group. However, NFR was not inhibited in any group. In fact, NFR increased for the E+C ($p=.02$) and E ($p<.001$) groups. Findings suggest that placebo-induced pain inhibition is not mediated by descending inhibition of spinal nociception and instead may be influenced by other cortical processes.

Disclosures: **Y.M. Guereca:** None. **B. Kuhn:** None. **S. Palit:** None. **J.L. Rhudy:** None.

Poster

604. Pain Physiology

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Topic: D.08. Pain

Support: The University of Tulsa Student Research Award

Title: Wearing video goggles inhibits spinal nociception

Authors: *E. W. LANNON, J. RHUDY;
The Univ. of Tulsa, Tulsa, OK

Abstract: Viewing a stimulated body part has been shown to result in inhibition of pain and supraspinal nociception. However, it is unknown whether this involves descending inhibition of spinal nociception. The present study attempts to examine this issue by measuring the nociceptive flexion reflex (NFR), a spinally mediated reflex in the leg that is evoked by painful stimulation. Because the NFR is highly correlated with painful stimulus intensity and subjective pain report it is often used as an indirect measure of spinal nociception that can be influenced by descending modulatory pathways. The current study used a within-subjects design to manipulate the participant's visual input while pain report (intensity/unpleasantness) and the NFR were measured in response to painful electric stimulations to the sural nerve. 13 healthy pain-free individuals (8 women) underwent three conditions in which their visual input was manipulated with the use of a video camera connected to video goggles (VG). In two conditions, participants received live video feedback of the stimulated body part (their leg) or the projector screen in front of them (control). In another condition, participants were asked to look at the screen in front of them without VG (as a control for wearing VG). Results indicated that viewing a stimulated body part did not change pain report (intensity/unpleasantness) or the NFR (ps>.05). However, wearing video goggles significantly reduced the NFR and pain intensity (ps<.05). These results suggest that wearing VG activates descending inhibition of spinal nociception which results in pain reduction.

Disclosures: E.W. Lannon: None. **J. Rhudy:** None.

Poster

604. Pain Physiology

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Program#/Poster#: 604.27/N13

Topic: D.08. Pain

Support: OCAST Grant HR12-100

Title: Predictors of placebo analgesia of pain and spinal nociception

Authors: *S. PALIT, Y. M. GUERECA, B. L. KUHN, J. L. RHUDY;
Univ. of Tulsa, Tulsa, OK

Abstract: Placebo analgesia refers to a sham treatment that results in pain reduction and is mediated by expectations for reduced pain and conditioning (e.g., inert treatment + pain relief). Nevertheless, individual differences in placebo response exist, and identifying its predictors may improve pain treatments. Several predictors have been previously identified, including optimism

(positive beliefs about future outcomes), expectation for pain relief, and reward motivation (e.g., drive towards a goal). However, these predictors have not been used together to determine which best predicts placebo response. Further, predictors of placebo analgesia of spinal nociception have yet to be examined. The current data were taken from a study of placebo analgesia that randomized 134 participants to 1 of 4 conditions: natural history (NH) control, conditioning (C), expectation (E), or expectation and conditioning (E+C). Suprathreshold stimulations were delivered to the ankle to evoke pain and the nociceptive flexion reflex (NFR; physiological measure of spinal nociception) before and after application of an inert cream. The E+C and E groups were told the cream was a "powerful painkiller" while the NH and C groups were told it was "sensor gel." Placebo response was defined as post- minus pre-cream changes in pain and NFR. Participants rated their expectation for pain relief following cream application. Individuals also completed the Life Orientation Test-Revised (LOT-R) and the Behavioral Inhibition System/Behavioral Approach System (BIS/BAS) scales to assess optimism and motivation, respectively. For the purposes of the present study, the NH group was excluded and all placebo groups (N = 104) were examined together to identify predictors of placebo response. Multiple regression indicated drive was a significant predictor of change in pain, such that higher drive was associated with greater post-pain ($p = .05$). The effect of optimism approached significance ($p = .06$), indicating a trend for higher optimism being related to less pain. Expectation of pain relief ($p = .01$) and drive ($p = .05$) were significant predictors of NFR change, such that higher expectation and higher drive were associated with increased NFR (nocebo response). These findings suggest that expectations and drive can have different associations with spinal and supraspinal outcomes. Drive is a significant predictor of nocebo response at both the supraspinal and spinal levels. In contrast, expectation for pain relief was only a significant predictor of spinal level nocebo.

Disclosures: **S. Palit:** None. **Y.M. Guereca:** None. **B.L. Kuhn:** None. **J.L. Rhudy:** None.

Poster

604. Pain Physiology

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Topic: D.08. Pain

Support: OCAST Grant HR12-100

Title: Heart rate variability is not associated with placebo analgesia

Authors: *B. KUHN[1], Y. GUERECA[2], S. PALIT[2], J. RHUDY[2];
[1]Psychology, [2]The Univ. of Tulsa, Tulsa, OK

Abstract: Placebo analgesia is pain reduction induced by a sham treatment. Heart rate variability (HRV) is a measure of autonomic nervous system control over the heart. Commonly used variables to analyze HRV are high frequency HRV (HF-HRV) and a ratio of low to high frequency HRV (LF/HF). HF-HRV is typically assessed from the frequency band corresponding to human respiration (.15-.40 Hz) and is believed to measure parasympathetic influence over the heart (from respiratory sinus arrhythmia), with larger values representing greater parasympathetic control. LF/HF is thought to reflect the balance of sympathetic and parasympathetic influences over cardiac functioning, with larger values representing greater sympathetic influence. Prior research has found HF-HRV is associated with decreased pain. The present study examined whether HRV metrics are associated with placebo analgesia. Specifically, we examined whether HRV is related to a change in pain ratings and the nociceptive flexion reflex (NFR; a physiological correlate of spinal nociceptive processing) following placebo manipulations. Participants were 139 healthy, pain-free individuals (69 females) involved in a placebo analgesia study. Individuals were randomly assigned to either a natural history control group (NH=35), an expectation only group (E=36), a conditioning only group (C=33), or an expectation plus conditioning group (EC=35). An inert cream was applied on two different occasions in the same day and pain and NFR were tested before and after each application. HRV metrics were assessed between the two cream applications. For our analysis, we computed a change score for both pain and NFR (post- minus pre-test). An ANOVA indicated that there were no group differences in HRV metrics (HF-HRV: $p = .13$; LF/HF: $p = .07$), although there was a trend for LF/HF to be lower in the E, C, and EC groups relative to NH (pairwise $ps < .05$). Additionally HRV was not significantly correlated with change in pain ratings (HF-HRV: $r = -.06$, $p = .46$; LF/HF: $r = .05$, $p = .60$) or change in NFR (HF-HRV: $r = .02$, $p = .87$; LF/HF: $r = -.04$, $p = .75$). These data suggest that placebo manipulations did not lead to group differences in HRV and that HRV is not a good predictor of placebo response.

Disclosures: B. Kuhn: None. **Y. Guereca:** None. **S. Palit:** None. **J. Rhudy:** None.

Poster

604. Pain Physiology

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Program#/Poster#: 604.29/N15

Topic: D.08. Pain

Title: Role of potassium channel TREK1 in formalin-induced acute and chronic nociception

Authors: *V. A. MARTÍNEZ-ROJAS, G. GARCÍA, A. HERNÁNDEZ MENDOZA, A. COVARRUBIAS CAMARILLO, J. MURBARTIÁN;
Cinvestav Sede Sur, Mexico City, Mexico

Abstract: TWIK-related 1 potassium channels (TREK1) are members of the two-pore domain potassium channel family that contribute to background conductances. TREK1 are expressed in nociceptors and their activity contributes to modulate nociception in acute inflammatory pain. However, the effects of this channel in chronic nociception are unknown. The aim of the present investigation was to assess the role of TREK1 in formalin-induced acute and chronic nociceptive responses in the rat. For this, rats were injected with formalin (1%, 50 μL, s.c.) in to dorsal hind paw. Acute nociception was determined by the number of flinches elicited by the injected paw every 5 min during 1 h. Chronic nociception was assessed 6 days after formalin injection by the application of von Frey filaments to the formalin-treated (ipsilateral) and untreated (contralateral) paw. Formalin injection produced acute nociceptive behaviors (1 h) followed by long-lasting evoked secondary allodynia and hyperalgesia in both paws (6 days). Local peripheral pre-treatment (-10 min) with the selective TREK1 activator BL-1249 (0.01-1 mM/paw) prevented formalin-induced flinching behavior in phase II but not phase I of the formalin test. Furthermore, local peripheral pre-treatment with BL-1249 (0.01-1 mM/paw) prevented in a dose-dependent manner the long-lasting evoked secondary mechanical allodynia and hyperalgesia in both paws. Local peripheral post-treatment (6th day after formalin injection) with BL-1249 (1 mM/paw) reversed formalin-induced secondary mechanical allodynia and hyperalgesia in both paws. TREK1 channels were detected in dorsal root ganglia and dorsal spinal cord of naïve rats without any significant change in TREK1 expression at 6 days after formalin injection. Our results implicate that TREK1 is present in sites related with nociceptive processing and modulates acute and chronic nociception induced by formalin in rats. VAM-R, GG and CC-A are Conacyt fellows.

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Poster

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Topic: D.08. Pain

Support: University of Catania

Title: Gender specific effects of fluoxetie, duloxetine and amitriptyline in pain behavior and spinal BDNF expression in mice

Authors: M. ZAMMATARO[1], M. BARRESI[1], S. MERLO[2], L. CUCCI[4], M. SORTINO[2], *S. CHIECHIO[3];
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Abstract: Antidepressant drugs are commonly used in various chronic pain syndromes. While there is a general consensus that the tricyclic antidepressant (TCA), amitriptyline, is the gold standard of analgesic antidepressants, analgesia obtained with selective serotonin reuptake inhibitors (SSRI) is less consistent. On the contrary, the dual serotonin/norepinephrine inhibitor (SNRI), duloxetine, has been shown to be efficacious both in persistent and inflammatory pain states. Although the serotonergic and noradrenergic systems have been implicated in the descending inhibitory control of pain and therefore in the analgesic effects of antidepressant drugs, in this study we evaluate whether brain-derived neurotrophic factor (BDNF) might also be involved. Long-term treatment with antidepressant drugs is known to increase hippocampal BDNF, a mechanism that supports the effectiveness of these drugs in depression. However, BDNF is also considered a central modulator in the development of pain sensitization. Furthermore, a number of studies point to a gender distinct effect of BDNF on depression-like behavior in rats, suggesting that there may be a sexual dimorphism in BDNF function. Based on this evidence, in this work we sought to evaluate the effect of long-term treatment of different classes of antidepressants on pain behavior and on BDNF expression in the spinal cord of male and female mice. We selected fluoxetine, amitriptyline and duloxetine as representative for SSRI, TCA, and SNRI classes of antidepressant drugs, respectively. Pain behavior and BDNF expression in the dorsal horn of the spinal cord were evaluated after a 21-day treatment (10 mg/kg, ip) with the three antidepressants both in male and female CD1 mice. Our results show a gender differentiated behavior in the formalin test of male and female littermate mice after a long-term administration. Specifically, a 21-day treatment with fluoxetine was unable to elicit analgesic response in both phases of the formalin test in male mice, but was able to significantly reduce the second phase of the formalin test in females. On the contrary, duloxetine and amitriptyline did not affect nocifensive behavior in the formalin test, in female mice, but they induced analgesia in males. Moreover, western blotting and immunohistochemistry analyses show that antidepressant drugs can differently modulate BDNF expression in the dorsal horn of male and female CD1 mice, suggesting that BDNF participates to pain modulation by antidepressant drugs in a gender specific manner.

Disclosures: **M. Zammataro:** None. **M. Barresi:** None. **S. Merlo:** None. **L. Cucci:** None. **M. Sortino:** None. **S. Chiechio:** None.

Poster

605. Somatosensory Signaling Mechanisms

Location: Hall A

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Topic: D.09. Tactile/Somatosensory Systems

Support: NIH Grant R01NS047715

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NIH Fellowship F32NS065718

Title: The biophysical basis of rapidly adapting mechanoreceptor currents in *C. elegans* touch receptor neurons

Authors: A. L. EASTWOOD[1], A. SANZENI[3], B. C. PETZOLD[2], S.-J. PARK[2], B. L. PRUITT[2], M. VERGASSOLA[3], *M. B. GOODMAN[1];
[1]Mol. and Cell. Physiol., [2]Mechanical Engin., Stanford Univ., Stanford, CA; [3]Dept. of Physics, Univ. of California at San Diego, San Diego, CA

Abstract: Our perceptions and reactions to the physical world are deeply rooted in our sense of touch and depend on somatosensory neurons that invade and innervate the skin. It is supposed that these neurons filter and convert the mechanical energy delivered in each touch into excitatory membrane currents carried by mechanoelectrical transduction (MeT) channels. Somatosensory neurons are classified according to their mechanical sensitivity and adaptation rate. The gentle touch receptor neurons (TRNs) of the nematode Caenorhabditis elegans have low thresholds for activation and adapt rapidly to both the application and removal of mechanical loads. These response dynamics are shared by other somatosensory neurons in *C. elegans* and by Pacinian and Meissner corpuscles in mammals. Yet, the mechanisms responsible for rapid adaptation and symmetrical on and off responses have remained enigmatic. To learn more, we developed the FALCON system and used it to record membrane current, applied force, and the resulting indentation in parallel. The system combines *in vivo* whole-cell patch clamp recording with a custom microcantilever and feedback control. Here, we use FALCON to show that MeT current amplitude increases with both indentation and stimulus rate. Rapid adaptation is robust to dramatic changes in body mechanics and persists under both force clamp and displacement clamp. Armed with these experimental findings, we also develop a physical model in which activation of the MeT channels that decorate TRN neurites is linked to body indentation via a viscoelastic element embedded in the animal's skin or cuticle. The model reproduces the observed indentation and rate sensitivity as well as the symmetrical on and off responses.

Because the model is independent of the molecular identity of the MeT channel and of any particular accessory structures, it provides a general mechanism for rapid adaptation that may be applicable to diverse mechanosensory cells across phyla and sensory modalities.

Disclosures: **A.L. Eastwood:** None. **A. Sanzeni:** None. **B.C. Petzold:** None. **S. Park:** None. **B.L. Pruitt:** None. **M. Vergassola:** None. **M.B. Goodman:** None.

Poster

605. Somatosensory Signaling Mechanisms

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Topic: D.09. Tactile/Somatosensory Systems

Support: NIH R01 N5047715

AHA 10POST4160127

NIH F32 NS065718

Title: The role of arachidonic acid containing-membranes in modulating mechanoreceptor currents *in vivo* in *C. elegans*

Authors: ***S. KATTA**[1], V. VÁSQUEZ[1,2], A. L. EASTWOOD[1], M. B. GOODMAN[1]; [1]Stanford Univ., Stanford, CA; [2]Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: Although we have known for two decades that bacterial mechanosensitive channels open in response to membrane tension, we have yet to determine what gates eukaryotic mechanotransducers. Given the variety and complexity of mechano-electrical transduction (MeT) apparatuses, we need a system in which we not only understand the identity of the MeT channel and its interacting partners, but can also explore the mechanics of the microenvironment and surrounding tissue. One such system is the MEC channel complex in *C. elegans* touch receptor neurons (TRNs). Previously, we determined that certain polyunsaturated fatty acids (PUFAs), contained in membrane phospholipids, affect behavioral responses to touch. In particular, we showed that *fat-1fat-4* worms, which lack arachidonic acid (AA), were partially defective in their responses to touch, and that supplementation of AA but not its metabolites rescued this phenotype (Vásquez et al., Cell Reports, 6:70-80, 2014). Optogenetic activation of the TRNs showed that the defect in *fat-1fat-4* worms was upstream of synaptic transmission and atomic force microscopy revealed that PUFAs modulate the mechanical properties of TRN plasma membranes. These results pointed to a change in either the initial mechanoreceptor

currents (MRCs) or the subsequent opening of voltage-gated calcium channels that amplify the MRC signal, but we had not yet characterized the currents in these animals. Here, we use *in vivo* whole-cell patch clamp electrophysiology to determine how the absence of AA in TRN membranes affects voltage-activated currents and MRCs. We combine a piezoelectric stack for driving the mechanical probe with a segmented photodiode system for measuring actual indentation (Peng et al., Neuron, 80:960-72, 2013), which allows us to apply larger indentations at a faster rate than was previously possible. We look at MRC kinetics and inactivation rates, the indentation-current curve, and the effect of indentation rate as we investigate the role of the membrane environment in MeT channel gating.

Disclosures: **S. Katta:** None. **V. Vásquez:** None. **A.L. Eastwood:** None. **M.B. Goodman:** None.

Poster

605. Somatosensory Signaling Mechanisms

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PAPPIT-DGAPA Grant IN200615

CONACyT Fellowship 317553 (ROM)

CONACyT Fellowship 233849 (YML)

Title: Segregated population of layer 5 sensorimotor cortex neurons projects to superficial and deeper laminae of the same spinal cord segment

Authors: *R. OLIVARES-MORENO[1], Y. MORENO-LOPEZ[1], L. CONCHA[1], M. CORDERO-ERAUSQUIN[2], G. ROJAS-PILONI[1];
[1]UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO, QUERETARO, Mexico; [2]Inst. des Neurosciences Cellulaires et Intégratives, Strasbourg, France

Abstract: Through projections to the spinal cord (CSP), the cortex modulates the sensory information flow as well as contributes to motor execution and control. However, it is not clear if corticospinal projections involved in these two different functions (sensory vs. motor) are strictly segregated or part of partially overlapping functional systems. In this work, we studied the

distribution of corticoespinal neurons (CSN) by injecting two different retrograde tracers in the spinal cord at the DH and intermediate zone-ventral horn the same segment in the rat. Our results show a partial segregation for both neonate and adults sensorimotor cortex, the main difference is that while in neonates this segregation extends to S1(probably due the immature development of corticospinal tract) in adults is more restricted to M1. On the other hand, in the adult about 93 % of the CSN reach DH while only 5 % arrive to deeper spinal cord laminae. This data suggests that M1 CSN drives in parallel distinct segmental neural circuits part of the sensory and pre-motor pathways, representing a new and additional level of sensorimotor integration.

Disclosures: R. Olivares-Moreno: None. **Y. Moreno-Lopez:** None. **L. Concha:** None. **M. Cordero-Erausquin:** None. **G. Rojas-Piloni:** None.

Poster

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PAPPIT-DGAPA Grant IN200615

CONACyT Fellowship 233849 (YML)

CONACyT Fellowship 317553 (ROM)

Title: Corticospinal segregated projections activates distinct segmental interneurons in rat spinal cord

Authors: Y. MORENO-LOPEZ[1], R. OLIVARES-MORENO[1], M. CORDERO-ERAUSQUIN[2], *G. ROJAS-PILONI[1];
[1]Univ. Natl. Autonoma Mexico, Queretaro, Mexico; [2]Dept. Nociception et Douleur, Inst. des Neurosciences Cellulaires et Intégratives, Strasbourg, France

Abstract: Corticospinal (CS) descending projection plays a major role in motor control by means of modulation of pre-motoneuron interneurons. Additionally this system is also involved in a selective and complex modulation of sensory information which is also important for the proper execution of movements. However, the segmental interneurons and the downstream networks driven by CS projection are poorly characterized. The objective of this study was the *in*

vivo electrophysiological characterization of neurons in the spinal cord that are modulated by CS tract in order to analyze if there are a different subpoblations of spinal interneurons related to sensory and motor control. We found two type of spinal interneurons responding to sensorimotor cortex according with their activation latency located in dorsal (laminae II-IV) and intermediate (lamina VII) grey matter. Both type of neurons receiving inputs from cortex also are activated by fast myelinated primary afferents. Our results suggest that the CS projection in parallel drives distinct segmental neural circuits all of them necessary for proper execution of volitive movements.

Disclosures: Y. Moreno-Lopez: None. **R. Olivares-Moreno:** None. **M. Cordero-Erausquin:** None. **G. Rojas-Piloni:** None.

Poster

605. Somatosensory Signaling Mechanisms

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Topic: D.09. Tactile/Somatosensory Systems

Support: NIH Grant P30 DA018310

Title: Peptidomic investigation of rat dorsal root ganglia

Authors: *E. G. TILLMAAND, N. YANG, E. V. ROMANOVA, S. S. RUBAKHIN, J. V. SWEEDLER;
Univ. of Illinois At Urbana-Champaign, Urbana, IL

Abstract: Peripheral neuropathies affect 2.4% of the population (Hughes, R. *BMJ*. 2002). Peripheral sensory disorders such as diabetic and HIV-induced neuropathies and post-herpetic neuralgia manifest in debilitating symptoms that include burning pain, numbness and tingling, reduced proprioception, and allodynia. To better understand what drives these disease states, the neurochemical mechanisms of sensory response in healthy neurons must first be understood. Primary sensory neurons, located in the dorsal root ganglia (DRG), are prime models for such studies. In-depth characterization of the peptide content within and released by these cells would improve our understanding of specific mechanisms of peripheral sensory information transmission as well as the functional role of sensory neurons and their peptides in both normal and pathological states. We performed peptidomic analyses of both whole DRGs and cultured DRG cells from *Rattus norvegicus* using liquid chromatography electrospray ionization Fourier transform mass spectrometry (LC-ESI-FT MS). In a peptidomic analysis of six sets of DRG

samples, *de novo* sequencing resulted in the identification of over 2500 peptides from 297 proteins. Neuropeptides derived from six prohormones: calcitonin gene-related peptide, calcitonin, osteocalcin, protachykinin-1, proSAAS, and secretogranin II were observed. To better understand the peptide content of cellular release, DRG cells were cultured in 2 mm diameter restricted spaces and stimulated using a high potassium extracellular media. Samples of releasates before, during, and after stimulation were collected from over 140 cell cultures developed from six rats. Matrix-assisted laser desorption/ionization time of flight MS analysis of the samples revealed 41 signals of interest. Molecular mass-matching of the signals to the LC-ESI-FT-MS analysis data sets revealed 24 known peptides from 20 protein precursors, including neurologically relevant proteins such as neurofilament heavy, medium, and light polypeptides, vimentin, high mobility group protein B1, gamma synuclein, and peptidyl-prolyl cis-trans isomerase FKBP1A, as well as periaxin and myelin protein P0, which are involved in glial cell function. Interestingly, one potential hemorphin peptide was observed. Hemorphins are known to activate opioid receptors and play a role in the anti-pain response (Honda, M. et al. *Jpn J Pharmacol.* 2001). This study provides information on the peptide contents of whole DRGs and cultured DRG cells and is a first step toward a more complete peptidomic characterization.

Disclosures: E.G. Tillmaand: None. **N. Yang:** None. **E.V. Romanova:** None. **S.S. Rubakhin:** None. **J.V. Sweedler:** None.

Poster

605. Somatosensory Signaling Mechanisms

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Topic: D.09. Tactile/Somatosensory Systems

Support: NIH Grants DC010900 and RR025012

Title: Reflexive voice pitch responses to laryngeal mechanosensory stimulation

Authors: *M. J. HAMMER, S. A. PALM, A. BHATTACHARYA;
Univ. of Wisconsin, Madison, WI

Abstract: I. INTRODUCTION: Evidence suggests that laryngeal mechanoreceptors provide perceptual and proprioceptive afference for a variety of essential human functions including airway protection, breathing, and voice. These stretch, touch, and pressure sensitive mechanoreceptors within the laryngeal mucosa appear to be exquisitely arranged for the rapid transmission of a constellation of movement and voice related afferent information. It has been

reasonably argued that mechanosensory and auditory mechanisms are each important for optimal voice control. However, our understanding of mechanosensory mechanisms remains incomplete. Therefore, our objectives were to test whether mechanosensory input to the laryngeal mucosa during vocalization evokes a reflexive voice pitch response and to determine whether the response size may be associated with stimulus magnitude. II. METHODS: The institutional ethics committee for the safety of human subjects approved this protocol; written informed consent was obtained from each participant. An endoscopic approach was used to deliver a 135ms pressure-calibrated air stimulus to the mucosa surrounding the arytenoid/corniculate cartilage within the larynx as each participant sustained the vowel "eeee". Each participant completed 10 trials at each of 5 stimulus pressures (2, 4, 6, 8, and 10 mmHg). The voice signal was recorded using a head-set microphone. Fundamental frequency (in Hz) was extracted from each raw voice acoustic signal and normalized by converting into cents (100 cents = 1 semitone) to enable us to average data across participants. III. RESULTS/DISCUSSION: We found that the mechanosensory stimulus consistently evoked a reflexive voice pitch response. We also observed an increase in response magnitude as stimulus pressure increased. The direction of these responses and the fact that response size was modulated by stimulus magnitude suggests that the vocal sensorimotor system may utilize input from laryngeal mechanoreceptors to correct for errors in vocal pitch. Therefore, our findings support the important role of mechanosensory input for fine voice control.

Disclosures: **M.J. Hammer:** None. **S.A. Palm:** None. **A. Bhattacharya:** None.

Poster

605. Somatosensory Signaling Mechanisms

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Topic: D.09. Tactile/Somatosensory Systems

Support: NSF DGE-1069104

Title: A multiphysics model of the pacinian corpuscle

Authors: ***J. QUINDLEN**[1], H. K. STOLARSKI[2], M. FLANDERS[3], V. H. BAROCAS[1]; [1]Biomed. Engin., [2]Civil Engin., [3]Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: The Pacinian corpuscle (PC) is a cutaneous mechanoreceptor located in the dermis. It responds to high frequency (20-1000 Hz), low amplitude vibrations. At the tip of a myelinated sensory axon, an unmyelinated neurite is surrounded by concentrically-aligned lamellae

separated by pressurized fluid. When a stimulus is applied to the PC, the deformation is passed through the lamellae, distorts the neurite, opens stretch-gated ion channels, and initiates a neural response. Loewenstein and Skalak (1966) proposed that the interaction between fluid and lamellae causes the PC to act as a high-pass filter, as compression of the PC causes viscous forces to develop due to fluid flow between lamellae. Fluid-lamellar interactions determine the subsequent deformation on the neurite. The first step in the modeling embedded PCs of different orientations at different depths in the skin. To create a model of the mechano-to-neural transduction process that accounts for fluid interactions, a finite-element mechanical model used a spherical PC as an approximation of its ellipsoidal shape. Shell and lubrication theories were used to reduce the problem dimension. The solid and fluid layers were coupled through fluid velocity and pressure. The PC was modeled as a series of 30 shells with a lubricating fluid between each shell and a central incompressible core. Lamellar thickness ranged from 0.1-0.4 μm, increasing with distance from the core. Pressure was applied to the outer shell at 1 Hz-10^8 Hz frequencies. The simulations calculated the ratio of displacements of the inner and outer shells, thus determining neurite stretch at various indentation amplitudes and frequencies. The model showed stretch amplification in layers close to the core, making it possible for the neurite to initiate a response to low amplitude stimuli. The mechanical model will be modified to incorporate the inner core of the PC in addition to the previously modeled outer core. The inner core contains approximately 60 closely packed lamellae that are bilaterally arranged on either side of the neurite, with longitudinally-oriented clefts. Since the current model approximates the PC as 30 concentric layers, the inner core will be included to capture the mechanics of the entire PC structure. The next step is to create a neural model that can input the neurite stretches calculated from the mechanical model and predict known response properties. The geometry of the neural model will be refined to incorporate the detailed morphology of the neurite, including its filopodia. The overall aim is to generate a skin vibration to action potential model including the global morphological characterization of the PC system of human hand.

Disclosures: **J. Quindlen:** None. **H.K. Stolarski:** None. **M. Flanders:** None. **V.H. Barocas:** None.

Poster

605. Somatosensory Signaling Mechanisms

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Topic: D.09. Tactile/Somatosensory Systems

Title: Cold temperature stimulates IP3R-mediated calcium release in skin cells

Authors: *S. E. PIERCE, N. W. BELLONO, E. OANCEA;
Brown Univ., Providence, RI

Abstract: While the temperature of internal organs is tightly regulated, human epidermal melanocytes (HEMs) are constantly exposed to the fluctuating temperatures of the external environment. Mechanisms for detecting and responding to such changes are important for preventing hypo and hyperthermia at the organismal level. Previous research suggests that responses to temperature are mediated by thermoreceptor neurons innervating the skin. In particular, transient receptor potential (TRP) channels have been implicated in the cold temperature response in sensory neurons, including TRPA1 (<17 degrees C) and TRPM8 (<22 degrees C). However, the mechanisms that allow skin cells to directly detect such changes remain unknown. Here, we investigated cold-temperature responses, defined as a temperature ramp from 22 degrees C to 12 degrees C, in human skin cells. Using fluorescence calcium imaging, we found cold-temperature evoked calcium responses in HEMs and a model melanoma cell line MeWo that were independent of extracellular calcium. These responses in melanocytes are up to 4.7-fold higher than in cell types that are not normally exposed to the external environment, such as human embryonic kidney (HEK) cells. Exposing these skin cell lines to cell-permeant TRPA1 and TRPM8 inhibitors had no effect on the temperature response. Therefore, in contrast to sensory neurons, TRP channels are likely not involved. Further fluorescence microscopy with SERCA inhibitors prevented any calcium response to cold temperature, implying that these responses are caused by calcium release from endoplasmic reticulum (ER) stores. Whole-cell patch clamp experiments with IP3R antagonists similarly blocked the response. Our results suggest that human melanocytes have a cold-activated signaling mechanism that is independent from neuronal ones, triggering an IP3R-mediated calcium release from the ER. This pathway could have important implications in temperature regulation and cold temperature related pathologies, such as cold urticaria.

Disclosures: **S.E. Pierce:** None. **N.W. Bellono:** None. **E. Oancea:** None.

Poster

605. Somatosensory Signaling Mechanisms

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Topic: D.09. Tactile/Somatosensory Systems

Support: DE000721

Title: Development of a screening platform for natriuretic peptide receptor 1 antagonists

Authors: H. SOLINSKI, S. MISHRA, J. HUANG, M. KRIEGBAUM, *M. HOON;
NIDCR, Bethesda, MD

Abstract: In mammals, a variety of different chemicals cause the sensation of itch. These chemical agents activate itch-specific primary sensory neurons in the skin. This information, in turn, is transmitted to second order neurons in the spinal cord. Interestingly, primary pruriceptors primarily use the neuropeptide natriuretic peptide B (NppB) to activate secondary pruriceptors via the NppB receptor Npr1. Thus, blockage of Npr1 is an attractive strategy to interfere with acute itch and may be useful in ameliorating some forms of chronic itch. However, there are no available potent and selective Npr1 antagonists. Therefore, we embarked on the development of a high-throughput screening platform for small molecule Npr1 antagonists. Specifically, we are expressing human Npr1 in HEK293 cells and detect its activation by measuring elevated cellular cGMP levels, generated by the enzymatic portion of Npr1. The assay currently undergoes primary high-throughput screening in a 1536-well format. Our future plans include *in vitro* validation of candidate molecules to ensure their specificity and direct action. Lastly, we hope to eventually test verified candidate molecules in mouse models for acute and chronic itch.

Disclosures: H. Solinski: None. **S. Mishra:** None. **J. Huang:** None. **M. Kriegbaum:** None. **M. Hoon:** None.

Poster

605. Somatosensory Signaling Mechanisms

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Topic: D.09. Tactile/Somatosensory Systems

Support: NRF-2012-0009675

NRF-2013R1A1A2011913

Title: TLR signaling in mast cells contributes to chronic pruritus in a rat model of atopic dermatitis

Authors: *T. HAN[1], H. LEE[1], J. LEE[1], S.-K. BACK[2], H. NA[1];
[1]Korea Univ. Col. Med., Seoul, Korea, Republic of; [2]Dept. of Pharmaceutics & Biotechnology, Col. of Med. Engineering, Konyang Univ., Chungnam, Korea, Republic of

Abstract: Chronic pruritusof atopic dermatitis (AD) causes the patients to scratch the affected skin and thereby deteriorates the disease. Thus, relieving pruritus has been accepted as an

optimal management of AD. In a series of our studies elucidating the pathophysiological mechanisms underlying AD using a rat model, we have found that enhanced responses of DRG neurons to serotonin released from mast cellscontribute topersistent pruritus of AD. Mast cells express a variety of Toll-like receptors (TLR) allowing the immune cells to recognizepathogen-associated molecules. Some of TLR ligands are endogenous molecules which are released from damagedor inflamed tissues. In the present study, we examined whether TLR signaling in mast cells plays a role in chronic pruritus of AD.Bone marrow mast cells (BMMC) were obtained from adult male rats and used for RT-PCR, quantitative real-time RT-PCR and serotonin ELISA. Of total 12 TLRs (TLR1 to TLR12) checked in the present study, 10 TLRs (TLR1 to TLR10) were expressed by BMMCof which mRNA expression of pro-inflammatory cytokines (IL-1β, TNF-α, IL-4, IL-5, IL-6 and IL-13) were significantly increased when stimulated by TLR ligands, such as LTA, LPS, polyI:C (pIC), and extract of necrotic neuronal cells. In addition, TLR-mediated activation of BMMC led to increase of serotonin content in the culture mediumwhich induced scratching behaviors when applied to the skin of naïve animals. Our results indicate that Toll-like receptor mediated activation of mast cell drives chronic pruritus by secreting serotonin and pro-inflammatory cytokines

Disclosures: **T. Han:** None. **H. Lee:** None. **J. Lee:** None. **S. Back:** None. **H. Na:** None.

Poster

605. Somatosensory Signaling Mechanisms

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Topic: D.09. Tactile/Somatosensory Systems

Support: NIH grant GM103770

Title: Transmembrane guanlylyl cyclases and CaMKI mediate thermosensory signaling and thermal acclimation

Authors: *Y. YU, A. TAKEISHI, V. HAPIAK, H. BELL, P. SENGUPTA;
Biol., Brandeis Univ., Waltham, MA

Abstract: Animals actively seek optimal temperatures for survival and reproduction. Unlike many organisms that exhibit a constant temperature preference, the preferred temperature of *C. elegans* is plastic, and set by their experience of their cultivation temperature. The AFD neurons are the primary thermosensory neurons in *C. elegans*, and drive thermosensory navigation behaviors on thermal gradients. Although the AFD neurons are known to respond to temperature

variations of as little as 0.01ºC, how worms sense temperature and set their temperature preference are still largely unknown. Thermosensation in AFD requires cGMP signaling, and molecules implicated in this pathway have been identified. These include receptor guanylyl cyclases (rGCs) expressed specifically in AFD, as well as phosphodiesterases, and cGMP-gated cation channels. To determine whether the AFD-specific rGCs GCY-8, GCY-18 and GCY-23 act as thermosensors, we misexpressed these rGCs singly or in combination in non-thermosensory neuron types, as well as in non-neuronal cells. We found that misexpression was sufficient to confer thermosensory responses onto both neuronal and non-neuronal cells. Each rGC appears to elicit temperature responses with different response thresholds. However, although the thermosensory response threshold in AFD adapts upon long-term exposure to a different temperature, the response threshold of rGC-misexpressing cells do not adapt similarly. Our work suggests that AFD-specific mechanisms including the function of the CMK-1 CaMKI enzyme may be important in regulating rGC gene expression and thermosensory adaptation in AFD. We are currently determining whether rGCs are sufficient to confer temperature responses upon heterologous expression, and identifying domains that may be sufficient to confer thermosensation onto other cell types.

Disclosures: Y. Yu: None. **A. Takeishi:** None. **V. Hapiak:** None. **H. Bell:** None. **P. Sengupta:** None.

Poster

605. Somatosensory Signaling Mechanisms

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 605.12/N28

Topic: D.09. Tactile/Somatosensory Systems

Title: Mechanisms underlying the scratching behavior induced by the activation of proteinase activated receptor-4 (PAR-4) in mice

Authors: *R. COSTA[1,2], E. S. PATRICIO[2], C. P. FIGUEIREDO[1], M. A. BICCA[2], G. C. SEGAT[2], E. S. FERNANDES[3], T. M. CUNHA[4], S. BEVAN[5], J. B. CALIXTO[2];
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Abstract: A role for proteinase-activated receptor-4 (PAR-4) was recently suggested in itch sensation. Here, we investigated the mechanisms underlying the pruriceptive actions of the selective PAR-4 agonist AYPGKF-NH_2 (AYP) in mice. Dorsal intradermal (i.d.) administration

of AYP elicited intense scratching behavior in mice, which was prevented by the selective PAR-4 antagonist (pepducin P4pal-10). PAR-4 was found to be co-expressed in 32% of tryptase-positive skin mast cells and AYP caused a 2-fold increase in mast cell degranulation. However, neither the treatment with cromolyn nor the deficiency of mast cells (WBB6F1-Kit$^{W/Wv}$ mice) were able to affect AYP-induced itch. PAR-4 was also found on gastrin releasing peptide (GRP)-positive neurons (pruriceptive fibers), and AYP-induced itch was reduced by the selective GRP receptor antagonist RC-3095. In addition, AYP evoked calcium influx in ~1.5% of cultured DRG neurons also sensitive to TRPV1 (capsaicin) and/or TRPA1 (AITC) agonists. Importantly, AYP-induced itch was reduced by treatment with either the selective TRPV1 (SB366791), TRPA1 (HC-030031) or NK1 (FK888) receptor antagonists. However, genetic loss of TRPV1, but not of TRPA1, diminished AYP-induced calcium influx in DRG neurons and the scratching behavior in mice. These findings provide evidence that PAR-4 activation by AYP causes pruriceptive itch in mice via a TRPV1/TRPA1-dependent mechanism. **Keywords:** PAR-4, scratching behavior, TRPV1 and TRPA1.

Disclosures: **R. Costa:** None. **E.S. Patricio:** None. **C.P. Figueiredo:** None. **M.A. Bicca:** None. **G.C. Segat:** None. **E.S. Fernandes:** None. **T.M. Cunha:** None. **S. Bevan:** None. **J.B. Calixto:** None.

Poster

605. Somatosensory Signaling Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: D.09. Tactile/Somatosensory Systems

Support: NIH Grant 1F31NS090909-01

NIH NINDS R01 NS061908

Title: Identification of interneurons that mediate nociception in *Drosophila* and are modulated by touch sensing neurons

Authors: ***A. BURGOS**[1], K. HONJO[2], C. QIAN[1], L. VENKATASUBRAMANIAN[1], L. MACPHERSON[1], D. GOHL[3], D. W. TRACEY[4], M. SILIES[5], W. GRUEBER[1]; [1]Columbia Univ., New York, NY; [2]Univ. of Tsukuba, Tsukuba, Japan; [3]Stanford Univ., Stanford, CA; [4]Indiana Univ., Bloomington, IN; [5]European Neurosci. Inst., Göttingen, Germany

Abstract: Nociceptive circuits are crucial for the detection and avoidance of harmful stimuli. Vertebrate studies have long proposed that mechanosensory input can modulate nociceptive circuits. One prominent example is the gate control theory where interneurons receiving input from nociceptive neurons can be inhibited by the activity of low-threshold mechanosensory neurons. Studying a relatively simple nervous system that has anatomically defined neural substrates, which can be reproducibly and simultaneously manipulated, can facilitate our understanding of somatosensory transduction and integration. In *Drosophila*, class IV (cIV) dendritic arborization neurons (da) function as the primary nociceptors. Upon exposure to noxious stimuli, larvae exhibit rapid withdrawal, or nocifensive, behaviors, which include 360° rolling, followed by an increase in crawling speed, or escape crawling. Although cIV sensory neurons have been shown to be necessary and sufficient for nociceptive behavior, the downstream neural circuitry underlying these behaviors is only beginning to be understood. We have identified a population of projection neurons, termed sPN1s, and provide anatomical and functional evidence that these neurons are functional targets of cIVs, and required for rapid nocifensive rolling behavior. We also show that sPN1s receive input from class III (cIII) gentle touch neurons, and that the activity of these neurons modulates sPN1-mediated nocifensive behavior. These results provide a starting point for functional dissection of diverse central circuits underlying nociception, and how these circuits are modulated by input from gentle touch receptors. We aim to identify additional neurons that participate in the sPN1 circuit to further probe integration of these modalities.

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Poster

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Title: Proprioceptive trigeminal neuron activity modulated by locus coeruleus by hyperpolarization-activated current inhibition

Authors: *J. WON[1,2], M. SAITO[2], Y. KANG[2,1], S. OH[1];
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Abstract: Locus coeruleus (LC) is a small population of noradrenergic neurons located in the rostral pons with projections widely distributed in the central nervous system, thereby involved in multiple brain functions such as arousal, attention and stress. The proprioceptive sensory neurons innervating jaw-closing muscles are exceptionally located in the mesencephalic trigeminal nucleus (MTN), which medially adjoins or intermingles with the LC nucleus. MTN neurons can display two distinct firing patterns by either relaying spike trains arising from muscle spindles or generating bursts in response to synaptic inputs. MTN neurons express hyperpolarization-activated current (I_h), which can attenuate EPSPs mediated by glutamate receptors, thereby suppressing bursts. We aimed to investigate whether I_h in MTN neurons would be affected by the activity of LC neurons. Coronal slice preparations were made from the brainstem of Wistar rats(p14-20). Dual or single whole-cell patch-clamp recordings were obtained from MTN and LC neurons or MTN neurons alone. LC neurons were activated by injection of current pulses(200-300pA, 1s) or microstimulation (3-5V, 0.2 ms, 100 Hz train for 1s) while I_h was induced in MTN neurons. Recorded neurons were labeled by injection of Lucifer yellow, and tyrosine hydroxylase immuno-staining was carried out to identify LC neurons. I_h was either reduced (n = 7/10) or showed no change (n = 3/10) during LC stimulation. In the presence of α2 adrenoceptor antagonist, I_h reduction was significantly suppressed (n = 4). Immuno-staining results showed that I_h reduction was seen in MTN neurons when tyrosine hydroxylase positive LC neurons were activated (dual recording, n = 4/4). I_h reduction in MTN neurons may enhance excitatory synaptic responses, which can lead to altered proprioception of the jaw-closing muscles. In view of our findings, enhanced activity of LC by prolonged stress may disturb the proprioceptive control for appropriate masticatory functions, thus leading to masticatory muscle disorders.

Disclosures: **J. Won:** None. **M. Saito:** None. **Y. Kang:** None. **S. Oh:** None.

Poster

605. Somatosensory Signaling Mechanisms

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Bundesministerium für Bildung und Forschung (Förderkennzeichen 01GQ1001A)

Neurocure

Gottfried Wilhelm Leibniz Prize

Title: Social touch and fast-spiking interneurons of rodent somatosensory cortex

Authors: *C. LENSCHOW, A. CLEMENS, M. BRECHT;
Bernstein Ctr. For Computat. Neurosci., Berlin, Germany

Abstract: Facial touch is an important behavior for social interaction in rodents. Neuronal responses to artificial stimulation of the whiskers have been extensively studied, however responses to facial touch appear to be quite different when stimulation occurs with natural, socially evoked stimuli. Interaction evoked action potential firing and membrane potential dynamics in the somatosensory cortex differ in males and females; additionally, socially evoked neuronal firing appears to depend on the estrus cycle in females. In order to more closely examine the mechanistic underpinnings of these sex-related differences, we performed chronic juxtacellular recordings in head-fixed male and female rats while monitoring the estrus phase of the females. We found that the neuronal response to social touch was dependent on cell-type, where fast-spiking (FS) interneurons in males and females responded better to social touch when compared with regular-spiking principal neurons. Upon closer examination of the physiological properties of FS neurons in freely cycling females, we found that the baseline firing and response to social touch in FS interneurons is cyclical in nature. In estrus, the baseline firing is highest and the response to social touch is the lowest. To determine a possible molecular mechanism for the observed cyclical pattern of neuronal behavior, we are currently searching for hormonally modulated targets that co-localize with fast-spiking neuronal markers. The outcome of these experiments will advance our understanding of how cortical processing is modulated by neuroencrinological signals and mediates socio-sexual behavior.

Disclosures: **C. Lenschow:** None. **A. Clemens:** None. **M. Brecht:** None.

Poster

605. Somatosensory Signaling Mechanisms

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XDB01020300

Title: Combination of physiological function with cellular character in single somatosensory neuron using *in vivo* whole-cell recording and quantitative single cell real-time PCR

Authors: *C.-L. LI[1], K.-C. LI[1], L. BAO[2], X. ZHANG[1];
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Abstract: The properties of dorsal root ganglion (DRG) neurons are defined by their responses to peripheral stimuli. Cellular characteristics of DRG neurons contribute to their physiological functions. Recently, the transcriptome of DRG neuron has been uncovered by single cell RNA-sequencing. However, there is still an obvious gap between cellular character and physiological function of DRG neuron. We intend to link physiological function directly with cell character of DRG neuron. We performed *in vivo* whole-cell patch clamp to record the response of lumbar 5 DRG neurons to cutaneous thermal (heat and cold) and mechanical (brush, pressure and pinch) stimuli in adult mouse. After recording, the internal solution was subjected to reverse transcription and amplification. Then we performed quantitative single cell real-time PCR to evaluate the gene expression level of neuronal markers. Recorded neuron was sorted into corresponding cluster according to their biomarkers. We found that the Nppb-positive neurons were sensitive to noxious heat and mechanical stimuli (pinch), but insensitive to innocuous mechanical stimuli. The Th-positive neurons were specifically response to innocuous mechanical stimuli (brush), sensitive to pressure and pinch, but not to heat and cold. The Mrgprd-positive neurons showed response to all stimuli with a preference to heat stimuli. These results provide a new understanding of physiological functions of somatosensory neurons.

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Poster

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Uppsala University

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Söderberg foundation

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Wiberg foundation

Bergwall foundation

Title: A neuronal brake on itch through metabotropic glutamate receptor activation

Authors: *F. B. FREITAG, K. ROGOZ, B. ARESH, H. PETTERSON, L. INGWALL, E. MAGNÚSDÓTTIR, H. ANDERSEN, C. NAGARAJA, K. KULLANDER, M. LAGERSTRÖM; Neurosci., Uppsala Univ., Uppsala, Sweden

Abstract: Aim: The aim of this study was to identify the possible involvement of inhibitory G-protein coupled metabotropic glutamate receptors in itch regulation. Methods: Itch behavior was assessed in mice injected with a mGluR agonist prior to i.d. injection of several histaminergic and non-histaminergic itch inducing agents. To confirm the inhibitory effect of activation of the mGluR on histamine activated peripheral neurons, calcium imaging was performed in DRG culture cells. Results: mGluR agonist treatment reduced itch behavior provoked by histamine, 48/80 and α-methyl serotonin. Histamine and α-methyl serotonin are both associated with the activation of the intracellular enzyme PLCß3 which we could confirm was co-expressed with the mGluR as well as Hrh1, indicating that the mGluR regulates histaminergic and PLCß3-associated itch. This inhibitory effect was functionally confirmed on a neuronal level, where mGluR agonist strongly modulated histamine calcium evoked responses. Conclusion: Here we show that peripheral histamine sensing neurons, which express the mGluR regulates itch through an inhibitory effect. This finding raises a potential alternative to treat itch in its chronic states, where a down-regulation of itch-related neuronal activity would be achieved through mGluR activation.

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Poster

605. Somatosensory Signaling Mechanisms

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Topic: D.09. Tactile/Somatosensory Systems

Support: HHMI

Title: A human deafness gene (TMC1) homolog regulates locomotion via multiple dendritic sensory neurons in *Drosophila* larvae

Authors: *W. ZHANG[1], S. MELTZER[1], D. ZANINI[2], J. LI[1], T. CHENG[1], M. C. GÖPFERT[2], L. Y. JAN[1], Y. JAN[1];
[1]HHMI/UCSF, San Francisco, CA; [2]Dept. of Cell. Neurobiology, Univ. of Göttingen, Göttingen, Germany

Abstract: *Drosophila* larvae exhibit rhythmic locomotion behavior, which is modulated by peripheral sensory neurons. The relative contributions of different sensory neurons in coordinating locomotion behavior have not yet been elucidated. Here we study the roles of two types of multiple dendritic neurons, class I da neurons and bd neurons, in regulating larval locomotion. *Drosophila* larvae exhibit spontaneous turning during locomotion to explore the environment. Acute activation of Class I and bd neurons led to an increase of this turning frequency. Conversely, silencing those neurons reduces the turning frequency (Correct?). These neurons are likely proprioceptor for body posture during locomotion as we found that they could be directly activated by body curvature. We further found dmTmc, a *Drosophila* homolog of the human deafness gene (Tmc1), is expressed in class I da neurons and bd neurons. Knocking down dmTmc expression in these neurons pheno-copied the behavioral defects caused by dmTmc mutations, which reduced turning during locomotion. The dmTmc mutants' behavioral defects could be rescued by expressing dmTMC in class I and bd neurons. Importantly, we could induce spontaneously active currents by heterologously expressing dmTmc in cell lines. Our results suggest that dmTmc, a putative channel gene, is required for normal functions of class I da neurons and bd neurons in regulating larval locomotion behaviors.

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Poster

605. Somatosensory Signaling Mechanisms

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Topic: D.09. Tactile/Somatosensory Systems

Title: Intimate Touch at a Distance

Authors: *R. KOPPARAJU[1,2], S.-H. LIN[1,3], Y.-R. CHENG[1,4], Y.-C. CHIEN[1], U. HOCHGESCHWENDER[5], C.-C. CHEN[1,6,2];
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Abstract: C-fiber low threshold mechanoreceptors (C-LTMR) mediate the discriminative and affective touch in the skin. Previous attempt to characterise the C-LTMR has been constrained by the inability to selectively activate those afferents without affecting other myelinated nerve fiber or C-mechanonociceptors *in vivo*. Taking advantage of tools in mouse genetic using Cre-LoxP system, Cre reporter transgenic and a novel chemical luminopsin (LMO3) design, we reported here an example to activate these C-LTMR specific either with blue light or a chemical compound. The LMO3 is designed by fusion of an extracellular ligand (coelenterazine: CTZ)-inducible light-generating protein (Gaussia luciferase) to a light-activated channelrhodopsin and an intracellular EYFP. Downstream the human synapxin promoter, we placed a floxed-STOP cassette before the LMO3 and the whole construct is target to the mouse Hipp11(H11) locus with Transcription activator-like effector nucleases technique (TALEN). After germline transmission, we crossed the LMO3 mouse with Mas1-related G protein-coupled receptor B4 (MrgprB4)-Cre and generated the MrgprB4-Cre::LMO3 double transgenic mice. In this mouse, LMO3 is selectively expressed in the MrgprB4-positive C-LTMRs. We examined the expression of LMO3 with anti-GFP immunofluorescence and colocalization with Cre reporter. Result indicated that LMO3 is faithfully target to the MrgprB4-positive neurons and voltage clamp confirm the respond of LMO3 by either the presence of CTZ or 473nm blue light. In subsequent behavioural study, we discovered a significance preference to blue light chamber in the MrgprB4-Cre:LMO3 mice. Our findings suggest that we can specially evoke the pleasant touch without touching them. Long-term goal is to reveal the pleasant somatosensory pathway in the central nervous system.

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Poster

605. Somatosensory Signaling Mechanisms

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Thermo Scientific, gifted antibodies

NOAA Fisheries

Title: Somatosensory function of the dermal papillae in humpback whale skin

Authors: *S. A. ELDRIDGE[1,2], F. MORTAZAVI[2], F. L. RICE[3], D. R. KETTEN[4,5], D. L. ROSENE[2];
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Abstract: The glabrous skin of Cetacea (whales, dolphins and porpoise) confronts different sensory challenges than terrestrial mammalian skin. Understanding species-specific adaptations may elucidate life history or habitat use, such as compression receptors that respond to hydrostatic pressure and dive depth. However, little is known about innervation in cetacean skin. The glabrous skin of terrestrial mammals has molecularly unique afferents associated with: the encapsulated, rapidly-adapting low threshold mechanoreceptor (LTMR) Meissner's corpuscles in the dermal papillae (light touch and low frequency vibrations), and Pacinian corpuscles in the reticular dermis (high frequency vibrations); the slowly-adapting LTMR Merkel cell neurite complex (MCNC) in the stratum basale (light touch); and free nerve endings (temperature, nociception and high threshold mechanosensation). Sensory end-organs are presumed essential for low threshold mechanoreception, but only the Pacinian corpuscle has been found in Cetacea, where they are limited to lips, eyelids and skin around the blow hole. We investigated innervation in flank skin biopsies collected from the baleen whale *Megaptera novaeangliae* (humpback whale) (NMFS Permit #15240). Immunohistochemistry was used to search for functionally implicated sensory afferents. Serial immuno-stained sections were imaged and

reconstructed to visualize fiber organization, morphology and location of ramified endings. Axons extended to the apical end of the papillae, and a putative MCNC was found. The diverse population of axons in the papillae was characterized as presumptive low- and high-threshold mechanoreceptors by molecular homology, morphology, axon diameter, Schwann cell association, and ending specializations. Histological stains also showed the cellular organization of tissues. In the 8 mm epidermis, the closely packed papillae were ~100μm in diameter and ~5 mm long. As in terrestrial skin, the connective tissue had elastic fibers and capillaries that ran the entire length of the papillae. In all species, dermal papillae are subject to mechanical forces transmitted by stretch, retraction and shear that occur within and between tissue layers. However, in cetacean skin, the dense interdigitation of the pencillate papillae and epidermal pegs suggest a dynamic system. In addition to their roles in homeostasis, we propose the dermal papillae function as inherent sensory accessory structures that house LTMR fibers and novel receptors, allow innervation to reach within 2-3 mm of the body surface, and amplify and filter signals through their semi-enclosed tubular form.

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Poster

605. Somatosensory Signaling Mechanisms

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Topic: D.09. Tactile/Somatosensory Systems

Support: Deutsche Forschungsgemeinschaft (DFG)

Title: Stiffened membrane by STOML3 for the sense of touch

Authors: ***Y. QI**[1,2], L. ANDOLFI[3], F. FRATTINI[1], M. LAZZARINO[3], J. HU[1];
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Abstract: Sensing force is crucial in maintaining the viability of all living cells. Despite its fundamental importance, how force is sensed at molecular level stays largely unknown. Stomatin-like protein-3 (STOML3) has been shown to be essential for touch sensation in mouse. However, the molecular mechanisms by which STOML3 contributes to mechanotransduction remain mysterious. Here we hypothesize that STOML3 tunes sensitivity of mechanically gated ion channel by controlling the membrane mechanical properties of sensory neuron through

recruiting cholesterol. First, we show STOML3 is detected in the cholesterol-rich membrane fractions. Electrophysiological studies using whole patch clamp recording show depletion of membrane cholesterol with Methyl-β-cyclodextrin, a cholesterol chelating agent, abolishes slowly adapting (SA) mechanosensitive currents and reduces the amplitude of rapidly adapting (RA) mechanosensitive currents in sensory neurons from C57BL/6N but not STOML3-/- mice. Second, a STOML3 mutant deficient in cholesterol binding fails to restore the mechanosensitivity of STOML3-/- sensory neurons. Third, through atomic force spectroscopy (AFS), we discover that sensory neurons from STOML3-/- mouse exhibit softer membrane and smaller membrane tension when compared to wild-type. Importantly, we demonstrate that an intact STOML3 is essential to maintain membrane mechanics to sensitize mechanically gated channel Piezo1 in heterologous system. Finally, using behavioral test, tactile allodynia could be attenuated by injecting Methyl-β-cyclodextrin in C57BL/6N but not STOML3-/- mice, suggesting that stiffened membrane by STOML3 is essential for the tactile sensitivity. Altogether, we suggest that STOML3, as a member of stomatin like protein family, via binding cholesterol, controls membrane mechanics, thus facilitates the force transfer and tunes the sensitivity of mechano-gated channels, including Piezo channels. Targeting the cholesterol associating site of STOML3 might offer a novel peripheral means of chronic pain control.

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Poster

605. Somatosensory Signaling Mechanisms

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Topic: D.09. Tactile/Somatosensory Systems

Support: MNiSW Grant 6420/B/P01/2011/40

Title: Fear conditioning induces expression of cannabinoid 1 receptors (CB1) in barrel cortex of adult mice

Authors: ***E. SIUCINSKA**, W. BRUTKOWSKI, T. BERNAS;
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Abstract: Three days of whisker-shock fear conditioning expands the representation of "trained" vibrissae, which can be demonstrated by labeling with 2-deoxyglucose in layer IV of the barrel cortex in primary somatosensory cortex (S1) of adult mice. Results also show that functional

reorganization of the barrel cortex induced inhibitory synaptogenesis, increased expression of GABA transporter 1, affected cholecystokinin interneurons (CCK) expression in the hollows of trained barrels. There is the well known fact that CCK are containing of CB1 receptors. The CB1-expressing GABAergic axon terminals formed symmetric synapses. Endocannabinoids are powerful mediators of the short and long-term forms of plasticity at synapses via retrograde activation of presynaptic the CB1 receptors. Therefore, it is important to determine the expression of CB1+ puncta in the barrel cortex of mice 24h after whisker-shock associative learning paradigm. We hypothesize that CB1 receptors action would be to modulate GABAergic transmission in this region. In the whisker-shock conditioning group and all controls (pseudoconditioning, whisker stimulation-alone, shock-alone, and naïve animals) precise location of layer IV cells were identified using Hoechst 33258 staining of tangential sections. A method using confocal microscopic stereology has been applied to quantify the numerical density of CB1+ puncta in trained and control barrel hollow cortex in all groups of animals. Trained barrel hollow cortex activation by whisker-shock conditioning lead to a significant increase in the expression of CB1+ puncta, whereas similar changes in expression of CB1+ puncta were not found in the control groups. Our findings suggest that increasing activity of endocannabinoid system following locally amplified density of CB1+ puncta may modulate GABAergic neurotransmission at the synapses 24h after fear conditioning-dependent plasticity in the S1. (Support Grant 6420/B/P01/2011/40 to ES).

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Poster

606. Motoneuron Excitability

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VA P01HD32

Title: Operant conditioning of cutaneous reflexes in freely moving rats: Initial development

Authors: *Y. CHEN[1,2], L. CHEN[1,2], J. R. WOLPAW[1,2,3], X. Y. CHEN[1,2];
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Abstract: Operant conditioning is a powerful method for inducing motor learning. Studies in both animals and humans have shown that H-reflex conditioning can change the neurons and synapses of the pathway physiologically and anatomically, and can thereby affect complex behaviors such as locomotion that use the pathway (Encyclopedia of Neuroscience, 7:225-233, 2009). Recent studies in rats and humans show that appropriate H-reflex conditioning improves locomotor function after spinal cord injury (SCI) or peripheral nerve injury (for review Front Integ Neurosci (2014) doi: 10.3389/fnint.2014.00025). To further broaden the scientific and clinical applications of operant conditioning, we are developing new operant conditioning protocols that can target beneficial plasticity to other CNS pathways. Cutaneous reflex (CR) pathways play important roles in normal locomotion (J Neurophysiol 63:1109-1117, 1990; J Neurosci 17:3804-3814, 1997; Physiol. Rev 86:89-154, 2006) and contribute to spasms and abnormal postures after SCI or in other disorders (Exp Brain Res 196: 341-351, 2009; J Physiol 104:230-238, 2010). We are seeking to learn whether an operant conditioning protocol might modify CR pathways to improve functional recovery. Rats are implanted with EMG electrodes in right biceps femoris (BF, knee flexor), soleus (SOL, ankle extensor), and tibialis anterior (TA, ankle flexor) muscles and a nerve cuff on the right posterior tibial nerve (PT). The wires from all electrodes pass subcutaneously to a head-mounted tether. When BF and AT EMG activity stays in a defined range for several sec, a PT nerve cuff stimulus elicits a CR in the BF and/or TA. PT stimulus amplitude is automatically adjusted by the computer to produce a stable M response in SOL throughout data collection. Each rat is first studied under the control mode for 20 days. It is then exposed to a conditioning mode for 50 days. Under the control mode, no reward is given. Under the CRup (i.e., to increase the CR) or CRdown (i.e., to decrease the CR) conditioning mode, a food-pellet reward is given 200 ms after PT nerve stimulation if the BF (or TA) CR (typically 10-18 ms after PT stimulation in BF) is more (CRup mode) or less (CRdown mode) than a criterion value. The effect of conditioning is determined by comparing average CR size for the final 10 days of up- or down-conditioning to average CR size for the final 10 days of control-mode exposure. Successful conditioning is defined as a change of ≥20% in the correct direction (Exp Brain Res 97:31-39, 1993; J Neurophysiol 73:411-415, 1995).

Disclosures: **Y. Chen:** None. **L. Chen:** None. **J.R. Wolpaw:** None. **X.Y. Chen:** None.

Poster

606. Motoneuron Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 606.02/N40

Topic: D.10. Spinal Cord Injury and Plasticity

Support: NIH HD36020(XYC)

NIH NS22189(JRW)

NIH NS061823(XYC&JRW)

NIH EB018783(JRW)

NIH HD032571(AWE)

NYS SCI Trust Fund (XYC)

VA P01HD32

Title: Inferior olive ablation markably changes spinal cord GABAergic circuitry and KCC2 expression on motoneuron

Authors: *Y. WANG[1,2], Y. CHEN[1,2], L. CHEN[1,2], J. R. WOLPAW[1,2,3], X. Y. CHEN[1,2]; [1]Wadsworth Ctr. NYS Dept Hlth. & SUNY, Albany, NY; [2]Natl. Ctr. for Adaptive Neurotechnologies, Albany, NY; [3]Dept of Neurology, Stratton VA Med. Ctr., Albany, NY

Abstract: The inferior olive (IO) and the cerebellum are essential for acquisition and long-term maintenance of a down-conditioned (i.e., smaller) H-reflex (HR) (Learn Mem 12: 248-254, 2005, 13: 208-215, 2006; SFN Abs 475.17, 2012). In normal rats, conditioned HR decrease is associated with more motoneuron GABAergic terminals and GABAergic interneurons in the ventral horn (Eur J Neurosci 23: 141-150, 2006; Neurosci Lett 452: 124-129, 2009). To further explore IO participation in HR decrease, we assessed in rats the impact on GAD65 and GAD67 GABAergic terminals and potassium-chloride co-transporter (KCC2) expression of IO ablation before or after HR down-conditioning. Rats were implanted with chronic EMG electrodes in right soleus (SOL) muscle and a nerve stimulating cuff on right posterior tibial nerve. Each rat underwent chemical IO ablation before (acquisition (AC) rats) or after (maintenance (MA) rats) a 50-day exposure to the HR down-conditioning protocol. After IO ablation, MA rats continued under the down-conditioning protocol for 100 more days. At the end of data collection, each rat was injected in right SOL with CTB-Fluor 488 and perfused 3 days later. Lumber spinal cord was sectioned (16 μm) and processed for GAD65, GAD67, and KCC2 immunoreactivity. GAD65 and GAD67-positive terminals on identified SOL motoneurons, KCC2 expression on the

motoneurons, and GAD67-positive interneurons in ventral horn were assessed in a blinded fashion with the NIH image J program. IO ablation prevented acquisition. HR size in AC rats at the end of down conditioning was 96(±6SEM)% of its initial (i.e., control-mode) value (P=0.48, paired t-test). In these AC rats, the number of GAD67 terminals, the size and immunoreactivity of GAD67 and GAD65 terminals, and the size and IR intensity of GAD67 interneurons in ventral horn were significantly decreased ($p<0.0001$ vs. Naïve Control (NC) rats). In MA rats, HR size immediately before IO ablation averaged 59(±5)% of initial value ($P<0.001$), rose to 75-80% in the next 12-14 days, remained there for ~40 days, and then rose over 10 days to above its initial value and remained high (158(±19)% for days 91-100 post-ablation (P=0.025 vs. initial)). In these MA rats, the numbers of GAD67 terminals and GAD67 interneurons were decreased ($p<0.05$ and $p<0.001$ vs NC, respectively). KCC2-IR on SOL motoneurons was significantly decreased in both AC and MA rats ($p<0.001$ vs NC for both). These results provide new insight into the complex hierarchy of brain and spinal cord plasticity that underlies the induction and maintenance of HR down-conditioning.

Disclosures: **Y. Wang:** None. **Y. Chen:** None. **L. Chen:** None. **J.R. Wolpaw:** None. **X.Y. Chen:** None.

Poster

606. Motoneuron Excitability

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Topic: D.10. Spinal Cord Injury and Plasticity

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NICHD/ 1P41EB018783(JRW)

NICHD/HD032571(AWE)

NYS SCI Trust Fund (XYC)

VA P01HD32

Title: H-reflex conditioning after transection of dorsal ascending (DA) tract disturbs key locomotor features in rats

Authors: *L. CHEN[1,2], Y. CHEN[1,2], X. X. YANG[1,2], Y. WANG[1,2], J. R. WOLPAW[1,2,3], X. Y. CHEN[1,2];
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Abstract: In normal rats, right soleus H-reflex (HR) conditioning affects locomotor EMG activity and kinematics but does not disturb key locomotor features (e.g., right/left symmetry in timing and hip height (J Neurosci 25:6898-6906, 2005)). According to the negotiated equilibrium hypothesis (Neuroscientist 16:532-549, 2010; nearby poster), locomotor features are preserved through an iterative process, a negotiation, in which the old behavior (i.e., locomotion) repeatedly induces compensatory plasticity that preserves its key features despite the plasticity concurrently induced by the new behavior (i.e., a larger or smaller HR). Ascending sensory input is thought to guide the brain in inducing this compensatory plasticity. If this is correct, HR conditioning should produce asymmetrical locomotion in rats in which ascending sensory input has been greatly reduced; and the severity of the asymmetry should be correlated with the magnitude of HR change. We tested this prediction. Under general anesthesia, 32 Sprague-Dawley rats were implanted with EMG electrodes in both solei and a nerve stimulating cuff on the right posterior tibial nerve. Thirty days later, they were exposed to an HR conditioning protocol (i.e., 20 days of control mode followed by 50 days of right soleus HR up- or down-conditioning mode). In each rat, the DA was transected bilaterally at T8-9 under anesthesia either 50 days before HR conditioning (Study 1), or at the end of 50 days of HR up- or down-conditioning, after which up- or down-conditioning continued for 50 more days (Study 2). Locomotor EMG activity, kinematics, and HRs were assessed before and after conditioning (Study 1), or before conditioning, after conditioning just before DA transection, and 50 days later (Study 2). DA transection itself did not affect the HR or disturb right/left step symmetry; and HR conditioning prior to DA transection did not affect step symmetry ($r=0.08$, $p=0.83$). In contrast, in DA-transected rats, HR up- or down-conditioning markedly affected step symmetry, and the magnitude of HR change induced by the conditioning strongly correlated with the magnitude of step asymmetry ($r=0.84$, $p=0.002$). These results indicate that HR conditioning in the absence of adequate ascending sensory information disturbs locomotion. Thus, they support the prediction of the negotiated equilibrium hypothesis: ascending sensory input is essential for inducing the compensatory plasticity in spinal cord and brain that ensures preservation of an old behavior (i.e., locomotion) when a new behavior (i.e., a larger or smaller HR) changes the spinal cord.

Disclosures: L. Chen: None. **Y. Chen:** None. **X.X. Yang:** None. **Y. Wang:** None. **J.R. Wolpaw:** None. **X.Y. Chen:** None.

Poster

606. Motoneuron Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 606.04/N42

Topic: D.10. Spinal Cord Injury and Plasticity

Support: College of Health Professions, Medical University of South Carolina

Title: Magnitude of reciprocal inhibition on plantarflexor H-reflex increases non-linearly with level of dorsiflexor muscle activity in non-neurologically impaired humans

Authors: J. LIANG, *R. L. SEGAL;
Dept of Hlth. Professions, Med. Univ. of South Carolina, Charleston, SC

Abstract: Reciprocal inhibition from ankle dorsiflexors (tibialis anterior, TA) onto plantarflexor (soleus, SOL) H-reflexes has been observed in non-impaired individuals. However, these findings were under resting conditions or at a single level of TA activity, and may not be generalizable across a range of TA activity. The objective of this study was to explore the association between the magnitude of TA muscle activity and the concurrent SOL H-reflex amplitude in order to more completely examine the reciprocal inhibitory relationship between TA activity and SOL H-reflexes. Participants were seated with knee flexed and feet strapped on a customized instrumented footplate with ankles in neutral position. At rest, we elicited a SOL H-reflex recruitment curve by increasing the stimulus intensity in small increments until a maximal H-reflex was obtained followed by attainment of a maximum M wave. From the recruitment curve, we identified the intensity needed to elicit a SOL H-reflex slightly smaller than the maximal H on the ascending limb of the recruitment curve. We then elicited 20 H-reflexes at this stimulus intensity at rest. Then, with visual feedback, participants generated various magnitudes of TA contractions within specified windows of TA muscle activity that varied randomly in blocks of small to large magnitudes. For each level of TA muscle activity, 20 SOL H-reflexes were elicited. For each trial, when participants maintained the TA activity in the target window for 1 second, an electrical pulse was delivered, eliciting a SOL H-reflex. To ensure consistency of stimulations, we monitored the corresponding M waves and adjusted the stimulus intensity to keep the M wave in the desired range across all trials. TA EMG activity prior to electrical stimulus and peak-to-peak amplitudes of the baseline and SOL H-reflexes were analyzed offline. The coefficient of determination (R^2) was used to examine the percentage of the total variance in SOL H-reflex amplitude that could be explained by the TA muscle activity. We observed a decrease in SOL H-reflex amplitude with increase in TA activity that levels out as TA activity continues to increase. Although both linear (R^2 0.57 to 0.78) and logarithmic (R^2 0.72 to 0.93)

fits result in high R^2 values, the relationship is best described with a logarithmic fit, indicating high probability of predicting SOL H-reflex amplitude based on magnitude of TA activity using the fitted logarithmic function. This modulatory relationship on the SOL H-reflex by the TA muscle potentially provides a more informative method to assess reciprocal Ia inhibition in neurologically-impaired nervous systems where contradictory findings have been reported.

Disclosures: J. Liang: None. **R.L. Segal:** None.

Poster

606. Motoneuron Excitability

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Topic: D.10. Spinal Cord Injury and Plasticity

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NIH EB018783(JRW)

NIH HD032571(AWE)

NYS SCI Trust Fund (XYC)

VAP01HD32

Title: Operant conditioning of motor evoked potential (MEP) in free moving rats: Initial study

Authors: *X. Y. CHEN[1,2], Y. CHEN[1,2], L. CHEN[1,2], Y. WANG[1,2], J. R. WOLPAW[1,2,3]; [1]Lab. Neural Injury and Repair, Wadsworth Ctr, NYS Dept Hlth. & SUNY, Albany, NY; [2]Natl. Ctr. for Adaptive Neurotechnologies, Albany, NY; [3]Dept of Neurology, Stratton VA Med. Ctr., Albany, NY

Abstract: Operant conditioning is a powerful method for inducing motor learning. In animals and humans H-reflex operant conditioning can change the neurons and synapses of the spinal reflex pathway physiologically and anatomically, and can thereby affect behaviors such as locomotion that use the pathway (Encyclo of Neurosci, 7:225-233, 2009). In both rats and humans appropriate H-reflex conditioning improves locomotor function after spinal cord injury

(SCI) or peripheral nerve injury (for review Front Integ Neurosci (2014) doi: 10.3389/fnint.2014.00025). To further broaden the scientific and clinical applications of operant conditioning, we are developing new operant conditioning protocols that can target beneficial plasticity to other CNS pathways. Corticospinal pathways play a key role in motor control and their impairment contributes greatly to the disabilities produced by SCI or other disorders (Eur J Neurosci 34:1839-1846, 2011; Neurorehabil Neural Repair 26:7-19, 2012). The motor evoked potential (MEP) recorded in a skeletal muscle after motor cortex stimulation reflects corticospinal pathway strength. We are seeking to learn whether an operant conditioning protocol can strengthen this connection in rats. Rats are implanted with EMG electrodes in right soleus (SOL) muscle, epidural recording electrodes over the dorsal surface at T8-9 of the spinal cord, and epidural stimulating electrodes over the dura of the left sensorimotor cortex (SMC) hind-limb area. The wires from all electrodes pass subcutaneously to a head-mounted tether. When soleus EMG stays in a defined range for several sec, SMC stimulation elicits a small SOL MEP. SMC stimulus amplitude is automatically adjusted by computer to maintain a constant small (i.e., threshold) cord volley throughout data collection (so that any MEP change noted can be confidently ascribed to change at the spinal level. Each rat is first studied under the control mode for 20 days. It is then exposed to the conditioning mode for 50 days. Under the control mode, no reward occurs. Under the MEPup (i.e., to increase the MEP) or MEPdown (i.e., to decrease the MEP) conditioning mode, a reward (a food pellet) is given 200 ms after SMC stimulation if the SOL MEP (typically 7.5-18 ms after stimulation) is more (MEPup mode) or less (MEPdown mode) than a criterion value. The effect of conditioning is determined by comparing average MEP size for the final 10 days of up- or down-conditioning to average MEP size for the final 10 days of control-mode exposure. Successful conditioning is defined as a change of ≥20% in the correct direction (Exp Brain Res 97:31-39, 1993; J Neurophysiol 73:411-415, 1995).

Disclosures: **X.Y. Chen:** None. **Y. Chen:** None. **L. Chen:** None. **Y. Wang:** None. **J.R. Wolpaw:** None.

Poster

606. Motoneuron Excitability

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Topic: D.10. Spinal Cord Injury and Plasticity

Support: NIH NS22189 (JRW)

NIH HD36020 (XYChen)

NIH NS061823 (XYChen&JRW)

NIH 1P41EB018783 (JRW)

HD032571(AWEnglish)

VA P01 HD32(JRW)

Title: The negotiated equilibrium hypothesis of spinal cord function

Authors: *J. R. WOLPAW[1,2,3];
[1]Wadsworth Center, NYS Dept of Hlth., Albany, NY; [2]Natl. Ctr. for Adaptive Neurotechnologies, Albany, NY; [3]Dept of Neurology, Stratton VA Med. Ctr., Albany, NY

Abstract: This hypothesis is a response to the question of how the spinal cord remains a reliable common pathway throughout life. Its impetus is a long series of studies of the CNS plasticity associated with acquisition of a simple motor behavior – a larger or smaller H-reflex – and the impact of that acquisition on an important older behavior – locomotion. Their results, together with other laboratory and clinical data, have led to the following hypothesis: Ø **Substrate and Maintenance of a Motor Behavior.** Throughout life, the CNS acquires and maintains a repertoire of motor behaviors. New motor learning induces plasticity in the brain that leads to plasticity in the spinal cord. Brain and spinal cord plasticity combine to produce and preserve satisfactory performance, which is defined by a set of key features (e.g., key locomotor features include right-left symmetry in step timing and hip height). Each time the behavior occurs, deviations from these features induce plasticity that reduces the deviations. Ø **Negotiation Among the Behaviors.** All the motor behaviors in the repertoire undergo this process concurrently. Each is an independent agent that repeatedly induces spinal cord (and brain) plasticity that preserves its key features despite the plasticity induced by other behaviors. The aggregate process is a negotiation among the behaviors. *They negotiate the properties of the spinal neurons and synapses that they all use.* This ongoing negotiation keeps spinal neuronal and synaptic properties in an equilibrium – a *negotiated equilibrium* – that serves all the behaviors. When new learning changes the spinal cord, it begins a new negotiation among the new behavior and the old behaviors. The outcome is a new equilibrium that serves all the behaviors in the expanded repertoire. While the new negotiation preserves key features of old behaviors, it may change their muscular and kinematic details. A new negotiation may also occur when CNS trauma or disease impairs old behaviors. In this case, the negotiation often fails to fully restore the key features of old behaviors. Ø **Therapeutic Value of a New Behavior.** When a behavior is impaired, new learning that targets appropriate plasticity to a spinal site important in the behavior can improve it. Furthermore, by changing the ongoing negotiation among behaviors, this targeted plasticity can lead to plasticity elsewhere that further improves the old behavior: the targeted plasticity can enable the old behavior to escape a suboptimal local

minimum and can thereby more nearly restore its key features. Thus, new learning that induces targeted plasticity could supplement other therapies and enhance functional recovery.

Disclosures: J.R. Wolpaw: None.

Poster

606. Motoneuron Excitability

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 606.07/N45

Topic: D.13. Motor Neurons and Muscle

Support: NIH NINDS R01 NS37822

Title: Recording of reticulospinal neurons to understand their participation in upper limb bilateral exertion

Authors: *A. M. BURNS[1,2], H. ADELI[3], J. BUFORD[4];
[1]Biomed. Engin., [3]Neurosci., [4]Physiol. and Cell Biol., [2]The Ohio State Univ., Columbus, OH

Abstract: Movements produced by patients recovering from stroke tend to reflect outputs typical of the reticulospinal system. This supports the concept of reticulospinal neuron participation in the recruitment of muscles otherwise impaired by stroke. Focusing on upper limb movement, a better understanding of the reticular formation's role in limb control can be ascertained through recording reticular neurons during a bimanual isometric force task. The hypothesis that neural activity in the reticulospinal system encodes the force of both upper limbs was tested by recording from electrodes in the pontomedullary reticular formation (PMRF) in two non-human primates, M. fascicularis, during a bimanual isometric force task similar to BATRAC (bilateral arm training with rhythmic auditory cueing) rehabilitation used for humans. The task used in this study involves the use of force-sensitive joysticks for the measurements of exertion and completion of the following four trial types: (1) bilateral pushing (2) bilateral pulling (3) right limb flexion with left limb extension (4) left limb flexion with right limb extension. A predetermined amount of force was required of the subject to complete each trial and receive a reward. Twenty-four EMG electrodes were placed in twelve upper limb and trunk muscles bilaterally to monitor flexion and extension. Principal component analysis was conducted on recorded PMRF spikes to isolate neurons to then determine facilitative and suppressive firing patterns for muscle flexion and extension. With respect to the location of recorded reticular neurons, we expect that ipsilateral flexion and contralateral extension patterns demonstrated in trials three and four will output the highest level of activity, while the opposite pattern (ipsilateral

extension and contralateral flexion) will output the lowest levels of activity, as suggested from our previous studies. The results from this study will contribute knowledge important for the understanding of reticulospinal participation in the control of movements in stroke rehabilitation therapies.

Disclosures: **A.M. Burns:** None. **H. Adeli:** None. **J. Buford:** None.

Poster

606. Motoneuron Excitability

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 606.08/N46

Topic: D.13. Motor Neurons and Muscle

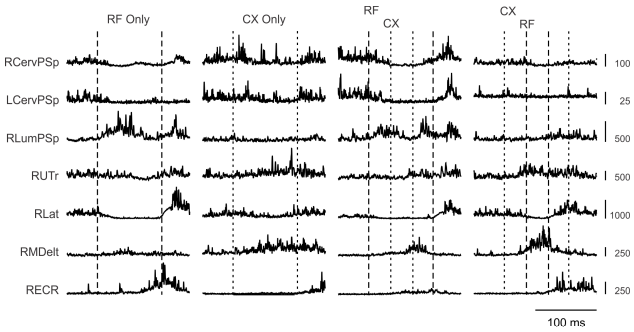
Support: NIH NINDS R01NS37822

Title: Combined corticospinal and reticulospinal effects on upper limb muscles: Cooperation and competition of motor systems uncovered using stimulus trains

Authors: *A. ORTIZ-ROSARIO[1,2], H. ADELI[2,3], J. A. BUFORD[4,2,3,1];
[1]Sch. of Hlth. & Rehabil. Sci., [2]Biomed. Engin., [3]Neurosci., [4]Div. of Physical Therapy, The Ohio State Univ., Columbus, OH

Abstract: The participation of muscle recruitment in the upper limb from the corticospinal and reticulospinal tracts has been studied separately. Their cooperation and competition for motor control, however, has not been explored experimentally. The purpose of this study is to present the effects of combined stimulus train pulses in both tracts to observe their effect on upper limb muscles of an awake, behaving primate (Macaca Fascicularis). Three cortical areas: primary motor cortex (M1), premotor area (PMA), and supplementary motor area (SMA), and two sides (left and right) of the ponto-medullary reticular formation (PMRF), the origin of the reticulospinal tract, were studied. Single and combined stimulus trains were applied on both areas eliciting muscle facilitation, suppression, or a combination of the two (Figure 1). One of the goals of this study is to observe the preferred pathways of these two regions and if events such as summation and gating are evident. Preliminary results show that on average 14% of events display summation of responses, and 5% of events displayed possible gating, mainly driven by the corticospinal tract. Understanding these pathways have far reaching consequences in rehabilitation approaches for stroke patients and improve the understanding of the intrinsic wiring of these two motor systems. **Figure 1: Example of the stimulation paradigm. RF**

denotes duration of stimulation on the PMRF, and CX denotes duration of stimulation on the motor cortex.



Disclosures: A. Ortiz-Rosario: None. **H. Adeli:** None. **J.A. Buford:** None.

Poster

606. Motoneuron Excitability

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 606.09/N47

Topic: D.13. Motor Neurons and Muscle

Support: NIH NINDS RO1 NS37822

Title: Interactions between corticospinal and reticulospinal outputs determine muscle response in the upper limbs and trunk as revealed with stimulus-triggered averaging

Authors: *S. HULBERT[1,2], H. ADELI[1,3], J. BUFORD[4,2];
[1]Biophysics, [3]Neurosci., [4]Physiolgy and Cell Biol., [2]The Ohio State Univ., Columbus, OH

Abstract: It is known that both corticospinal and reticulospinal tracts individually contribute to the stability and movement of the upper limbs and trunk. Using stimulus-triggered averaging (StimTA) of motor cortex and pontomedullary reticular formation (PMFR) outputs, we tested the hypothesis that these regions also interact to produce effects (suppression or facilitation) in the upper limbs and trunk. In our paired pulse paradigm, three areas of the cortex-primary motor cortex (M1), supplementary motor area (SMA), and dorsal premotor area (PMA)-were electrically stimulated at varying time shifts with respect to the electrical stimulation of either the right or left PMRF during a bilateral reaching task. Specifically, three paradigms were used: 1) Cortical area stimulated before PMRF, 2) Both areas stimulated simultaneously, 3) The PMRF stimulated before the cortical area. These experiments were conducted in three non-human primates, M. fascicularis. We studied 12 bilateral pairs of muscles in the upper limbs and trunk.

By comparing EMG results from the individual stimulation of the cortex or the PMRF to EMG results from the paired pulse paradigms, we were able to identify patterns that were indicative of dominant contribution from the PMRF or the cortex. We were also able to identify several patterns associated with summation or gating of the signals from the two brain regions. Preliminary results show that, of all patterns identified, about 22.84% are attributed to either PMRF or cortical activation alone, while the remaining patterns are associated with summation, gating, or other interactions between the regions. Results will be presented with respect to differences between cortical motor areas as they interact with the PMRF in the ipsilateral and contralateral limb. Taken together, these results show that corticospinal and reticulospinal systems can interact to produce muscle recruitment. Therefore, a systems approach is needed to fully understand the outputs of these motor systems.

Disclosures: S. Hulbert: None. **H. Adeli:** None. **J. Buford:** None.

Poster

606. Motoneuron Excitability

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Topic: D.10. Spinal Cord Injury and Plasticity

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Owsley Brown Frazier Chair in Neurological Rehabilitation Endowment

Russian Foundation for Basic Research Grant 13-04-12030 ofi-m

Title: Identifying supraspinal influences on lumbosacral motor neuron excitability after spinal cord injury: Effects of galvanic vestibular stimulation and acoustic startle reflex on MMR amplitude in leg muscles

Authors: A. MINK[1,4], D. SAYENKO[5], D. ATKINSON[2,4], Y. GERASIMENKO[5,6], S. HARKEMA[3,4], *.. .. . [1];

[1]Physiol. and Biophysics, [2]Anatom. Sci. and Neurobio., [3]Neurolog. Surgery, Univ. of Louisville, Louisville, KY; [4]Neurosci. Collaborative Center, Frazier Rehab Inst., Louisville, KY; [5]Dept. of Integrative Biol. and Physiol., UCLA, Los Angeles, CA; [6]Pavlov Inst. of Physiol., St. Petersburg, Russian Federation

Abstract: In the presence of epidural stimulation, individuals with complete motor paralysis after spinal cord injury (SCI) have shown the ability to voluntarily execute movement in the lower limbs, suggesting descending connections may have existed since the time of injury that were not detected clinically. Currently these pathways cannot be determined due to a lack of sensitive and quantitative measures. The purpose of this study is to develop a tool capable of assessing the viability of descending supraspinal pathways in humans with SCI. Multi-segmental monosynaptic reflexes (MMR) were evoked via transcutaneous electrical stimulation over the lumbosacral enlargement while lying in a supine position (n=13, 4 AIS A, 2 AIS B, 4 AIS C, 3 AIS D). Electromyographic activity was recorded in bilateral rectus femoris, vastus lateralis, medial hamstrings, tibialis anterior, medial gastrocnemius, soleus, and adductor hallucis brevis. MMRs were conditioned by an auditory stimulus (30 ms tone of 90dB @ 700Hz) delivered using binaural headphones to elicit the acoustic startle reflex (ASR) for evaluation of the reticulospinal pathway. MMRs were conditioned with galvanic vestibular stimulation (GVS) (rectangular pulses, 300ms) directly over the mastoid processes for evaluation of the vestibulospinal pathway. Condition-test intervals (CTI) ranging from 60-300 ms were used. Conditioning of lower limb muscles varied depending on severity of injury. Preliminary results indicate conditioning is present in at least 1 muscle in 13/13 participants in both GVS and ASR conditions. With GVS conditioning, 1/13 participants had all muscles conditioned, whereas with ASR conditioning, 2/13 participants had all muscles conditioned. Facilitation was most robust at CTI's of 140 ms and 190 ms with GVS conditioning and CTI's of 90 ms and 110 ms in ASR conditioning. This method of evaluating descending translesion pathways in SCI population may have potential in more effectively diagnosing individuals after neurological injury. This work was funded by: Frazier Rehab Institute and Kentucky One Health Kentucky Spinal Cord & Head Injury Research Trust Grant no. 11-7 Helmsley Foundation Grant #2011PG-MED011 Commonwealth of Kentucky Challenge for Excellence Trust Fund National Institute of General Medical Sciences Grant 8 P30 GM-103507 Owsley Brown Frazier Chair in Neurological Rehabilitation Endowment Russian Foundation for Basic Research Grant 13-04-12030 ofi-m Russian Scientific Fund Project Nos. 14-45-00024

Disclosures: A. Mink: None. **D. Sayenko:** None. **D. Atkinson:** None. **Y. Gerasimenko:** None. **S. Harkema:** None. **.... .:** None.

Poster

606. Motoneuron Excitability

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Topic: D.10. Spinal Cord Injury and Plasticity

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Owsley Brown Frazier Chair in Neurological Rehabilitation Endowment

Russian Foundation for Basic Research Grant 13-04-12030 ofi-m

Title: Transcutaneous spinal cord stimulation as a tool to investigate function of vestibulospinal, reticulospinal, and corticospinal descending pathways

Authors: *D. SAYENKO[1], D. ATKINSON[2,3], A. MINK[2,4], K. GURLEY[6], Y. GERASIMENKO[1,7], S. HARKEMA[2,5];
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Abstract: Quantification of the function of the descending vestibulospinal, reticulospinal, and corticospinal pathways is critical to understanding the connectivity and neuroplasticity in the central nervous system. Previous works have examined the effects of galvanic vestibular stimulation (GVS), auditory startle response (ASR), and transcranial magnetic stimulation (TMS) at the spinal level using the soleus H-reflex to assess motor neuron excitability. The H-reflex is limited in that it only provides information from unilateral spinal segments projecting to a single muscle. The present study was designed to systematically investigate the bilateral effects of the multi-segmental convergence of the vestibulospinal, reticulospinal, and corticospinal pathways on lumbosacral motor pools, using transcutaneous electrical spinal cord stimulation (TESS). We hypothesized that modulation of spinal motor output due to the convergence of descending and afferent volleys will depend on the specific pathway tested, as well as on the delay between the conditioning and test stimuli. Spinally evoked motor potentials were recorded in non-injured individuals using TESS, delivered over the intra-spinous space between the spinous processes of the T10 and T12 vertebrae, with subjects lying in a supine position.

Reponses were recorded via surface electrodes in vastus lateralis, medial hamstrings, tibialis anterior, and soleus muscles bilaterally. Vestibulospinal, reticulospinal, and corticospinal pathways were evaluated using conditioning binaural GVS (200 ms, up to 4 mA), ASR (30 ms, 90 dB, 700 Hz), and TMS (sub- and supra-motor threshold intensity), respectively, at different conditioning-test intervals (CTI). The conditioning stimulation resulted in the most robust facilitation at CTI between 90 and 160 ms following GVS and ASR, and at CTI between 10 and 25 ms and 90 and 140 ms following TMS. These results demonstrate that the lumbosacral motor pools can interact with the supraspinal descending volleys to facilitate the motor response. This method of investigating the descending supraspinal pathways allows objective quantification of the multi-segmental convergence of the vestibulospinal, reticulospinal, and corticospinal descending pathways with lumbosacral motor pools. Ultimately, this approach may provide a way to monitor and predict neuronal network plasticity associated with motor learning and functional recovery.

Disclosures: **D. Sayenko:** None. **D. Atkinson:** None. **A. Mink:** None. **K. Gurley:** None. **Y. Gerasimenko:** None. **S. Harkema:** None.

Poster

606. Motoneuron Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 606.12/O2

Topic: D.10. Spinal Cord Injury and Plasticity

Support: Frazier Rehab Institute and Kentucky One Health

Kentucky Spinal Cord & Head Injury Research Trust Grant no. 11-7

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Owsley Brown Frazier Chair in Neurological Rehabilitation Endowment

Russian Foundation for Basic Research Grant 13-04-12030 ofi-m

Title: Identifying descending propriospinal influence on lumbosacral motor neuron excitability after spinal cord injury: Effects of ulnar nerve stimulation on MMR amplitude in leg muscles

Authors: *D. A. ATKINSON[1,4], D. G. SAYENKO[5], A. MINK[2,4], K. GURLEY[6], V. SMITH[3], Y. P. GERASIMENKO[5,7], S. J. HARKEMA[3,4];
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Abstract: Ongoing studies of the effects of spinal cord epidural stimulation in human spinal cord injury (SCI) suggest the presence of descending neural influence which cannot be detected using current methods of SCI evaluation1. Electrophysiological assessments of descending pathways, such as the long propriospinal pathways, provide an alternative technique for assessing residual descending influence on motor neuron excitability below the level of lesion. The present study was designed to determine whether descending influence on lumbosacral motor neuron excitability could be detected via the effects of ulnar nerve stimulation on multi-segmental muscle responses (MMRs) of leg muscles. MMRs were evoked in 14 spinal cord injured participants (3 AIS As, 4 Bs, 4 Cs, and 3Ds) by transcutaneous electrical stimulation over the lumbosacral enlargement while lying in supine. MMRs were recorded via surface electrodes in bilateral rectus femoris, vastus lateralis, medial hamstrings, tibialis anterior, gastrocnemius, soleus, and adductor hallucis brevis muscles. MMRs were conditioned by non-noxious electrical stimulation of the ulnar nerve at a range of condition-test intervals (40-300ms). A functional neurophysiological assessment (FNPA)3 of volitional muscle activation and the International Society for Neurological Classification of Spinal Cord Injury (ISNCSCI) exam2 were also performed to assess volitional supraspinal drive to muscles below the level of injury. Conditioning stimulation delivered to the ulnar nerve resulted in facilitation of MMR amplitudes in at least one muscle group in 10/14 participants, with all muscles being facilitated in 3 participants. The condition-test intervals which most frequently and distinctly caused facilitation ranged from 90-140 ms. MMR modulation revealed descending influence on motor neuron pools below the level of SCI, which was not detectable during voluntary muscle activation attempts (assessed by FNPA and ISNCSCI exam) in 5 participants; MMR modulation was always seen in individuals (n=6) who demonstrated volitional activation of leg muscle(s). This method of assessing descending propriospinal influence on lumbosacral motor neuron excitability allows quantification of pathway-specific contributions to spinal excitability in multiple bilateral leg muscles, which are not detected by other methods. Results of this study, in conjunction with ongoing experiments involving reticulospinal, vestibulospinal, and corticospinal pathway modulation of MMRs, may aid in understanding the neurophysiology mediating voluntary movement observed in the presence of epidural stimulation after human SCI.

Disclosures: D.A. Atkinson: None. **D.G. Sayenko:** None. **A. Mink:** None. **K. Gurley:** None. **V. Smith:** None. **Y.P. Gerasimenko:** None. **S.J. Harkema:** None.

Poster

606. Motoneuron Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 606.13/O3

Topic: D.13. Motor Neurons and Muscle

Support: CONACYT Grant 128125

Title: Modulation of motoneuron excitability by α5GABAA receptors

Authors: *M. CANTO-BUSTOS[1], E. LOEZA-ALCOCER[2], R. FELIX[3], R. DELGADO-LEZAMA[2];
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Abstract: The γ-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. By activating synaptic and extrasynaptic specific receptors GABA can regulate neuronal activity. GABAA receptors are pentameric complexes of a diversity of subunits (α1-6, β1-3, γ1-3, δ, ρ1-3, ε, θ, and π), each with unique developmental and regional patterns of expression and distinctive biophysical and pharmacological properties. It is generally accepted that extrasynaptic GABAA receptors expressed in the cell body, dendrites and axons of neurons are tonically activated by GABA present in the extracellular space. Activation of these receptors produces a persistent conductance with several functional consequences. In this work we show that α5GABAA receptors are tonically active in motoneurons and modulate synaptic transmission between these cells and the funiculus dorsolateral terminals (FDL), in an *in vitro* preparation of the turtle spinal cord. Our results indicate that application of L-655,708 (inverse agonist with high affinity for the α5 subunit) inhibit α5GABAA receptor activity and in consequence produces the increase of monosynaptic excitatory postsynaptic potentials (EPSPs) and changes in the electrophysiological properties of motoneurons. These changes include an increase in input resistance and in the time constant, though the membrane potential remained constant. Furthermore, there was an increase in motoneuron excitability, because the rheobase was lower in the presence of L-655,708 than in the control condition. Finally, the presence of the α5GABAA receptor subunit in turtle motoneurons was confirmed by immunohistochemistry. We conclude that the tonic activity of postsynaptic α5GABAA receptors regulates the synaptic intensity in the synapses between the dorsolateral funiculus and the motoneurons and also regulates the firing of action potentials of turtle motoneurons.

Disclosures: M. Canto-Bustos: None. **E. Loeza-Alcocer:** None. **R. Felix:** None. **R. Delgado-Lezama:** None.

Poster

606. Motoneuron Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 606.14/O4

Topic: D.13. Motor Neurons and Muscle

Support: NIH Grant 082354

Title: Increasing Motoneuron persistent inward current as treatment for Sepsis-Induced Weakness

Authors: *M. M. RICH[1], P. NARDELLI[2], R. POWERS[3], T. COPE[2];
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Abstract: Despite years of study, the mechanisms underlying intensive care unit acquired weakness (ICUAW) remain unclear. Earlier studies had suggested myopathy and neuropathy were the primary causes of weakness. However, we recently identified a novel contributor to weakness in patients: difficulty with recruitment of motor units. Using the rat cecal ligation and puncture model of sepsis we found that a defect in motoneuron (MN) excitability is an important contributor to weakness induced by sepsis (Nardelli et al., 2013). The defect in MN excitability was not appreciable from firing threshold of single action potentials. Instead the defect was apparent only when MNs were driven to fire repetitively. During a 5s injection of current, septic MNs fired erratically with pauses of up to several seconds such that force generation by individual motor units was reduced by 80%. These data suggest that inability to sustain MN firing may be the primary mechanism underlying sepsis-induced weakness. The ability of MNs to repetitively fire is dependent on subthreshold persistent inward current (PIC). We examined the membrane depolarization leading up to spike initiation and found dramatic differences between control and septic MNs. In control MNs the approach to threshold was smooth and continuous. In septic MNs, there were oscillations during the approach to threshold such that the timing between spikes was variable and firing was inconsistent. Computer simulation of the defect in repetitive firing of septic MNs was possible with either a decrease in PIC or an increase in subthreshold voltage-gated K conductance. We wished to determine whether reducing the ratio of PIC to subthreshold K conductance could selectively impair repetitive firing of MNs *in vivo*. Using dynamic clamp of MNs we either subtracted PIC or increased subthreshold K in control MNs. Either manipulation was sufficient to induce septic-like deficits in repetitive firing. We next used dynamic clamp to either increase PIC or decrease subthreshold K conductance in

septic MNs and found that either manipulation was sufficient to correct repetitive firing such that that failure of muscle force generation was fully reversed. Our data suggest that increasing the ratio of PIC to subthreshold K may provide effective therapy to treat ICU acquired weakness in patients. Reference Nardelli P, Khan J, Powers R, Cope TC, Rich MM (2013) Reduced motoneuron excitability in a rat model of sepsis. J Neurophysiol 109:1775-1781.

Disclosures: **M.M. Rich:** None. **P. Nardelli:** None. **R. Powers:** None. **T. Cope:** None.

Poster

606. Motoneuron Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 606.15/O5

Topic: D.13. Motor Neurons and Muscle

Support: NSERC Grant 386601

Title: Estimates of persistent inward current in human soleus motor units decline during fatigue

Authors: K. MENDES, *J. M. KALMAR;
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Abstract: Persistent inward currents (PIC) prolong and amplify the response of spinal motor neurons to synaptic input and are important for motor output. These currents, which are increased by monoaminergeric drive and reduced with inhibitory inputs, are thought to be both state and task dependent. We hypothesized that PIC would decline during fatigue either through a decrease in monoaminergic drive or an increase in inhibitory input to spinal motor neurons. If reductions in estimated PIC are due to fatigue-induced changes in reciprocal inhibition (RI), then brief stimulation of the nerve innervating the antagonist muscle should decrease estimates of PIC prior to fatigue and reduce the subsequent decline during fatigue. Motor unit firing was recorded from low threshold soleus motor units. PIC was estimated during isometric, plantarflexion, triangular-ramp contractions using the paired motor unit technique, which uses the difference between the firing rate (ΔF) of a low threshold "control" motor unit at the recruitment and derecruitment of a higher threshold "test" unit. ΔF estimates of PIC were made before, between, and after sets of fatiguing contractions, and at the same time points on a no-fatigue control day in this repeated-measures study. ΔF was significantly reduced throughout the last half of the fatigue protocol ($p<0.01$), and returned to baseline after a recovery period. No changes in ΔF occurred over the course of the control protocol. On each day, RI was elicited via common peroneal nerve stimulation just before peak force during alternate ramps over the course of the protocol. ΔF

estimates of PIC were lower for these ramps compared to ramps without stimulation ($p<0.05$), and did not decline over the course of the fatigue protocol. These findings suggest PIC declines with fatiguing muscle activity, possibly due to afferent inhibition.

Disclosures: K. Mendes: None. **J.M. Kalmar:** None.

Poster

606. Motoneuron Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 606.16/O6

Topic: D.13. Motor Neurons and Muscle

Support: NIH Grant 5K12HD001097-15

Title: Is motor neuron excitability modulated by sex hormones across the menstrual cycle ?

Authors: E. K. CASEY[1], M. E. REESE[2], E. OKAFOR[2], D. CHUN[2], C. GAGNON[2], F. F. NIGL[2], *Y. Y. DHAHER[3];
[1]Family Med., Drexel Univ. Col. of Med., philadelphia, PA; [2]The rehabilitation Inst. of Chicago, Chicago, IL; [3]Northwestern Univ., Mount Prospect, IL

Abstract: The significant sex-disparity in sports-related knee injuries may be due to underlying differences in motor control. While the development of sex-specific movement patterns is likely multi-factorial, there is significant interest in the potential modulatory role of sex hormones. We have demonstrated that the muscle stretch reflex (MSR) changes throughout the menstrual cycle; however, further exploration is necessary to determine the origin of this change. This study examined the Hoffman Reflex (HR), electrical analogue of the MSR, across the menstrual cycle. Our aim was to measure motoneuron excitability across the menstrual and oral contraceptive pill cycle. Our hypothesis was that we would see an increase in motoneuron excitability during the peri-ovulatory phase in regularly menstruating women, due to the excitatory effects of the unopposed peak in estrogen concentration prior to ovulation. In addition, we hypothesized that the magnitude of change would be greater in eumenorrheic women with greater changes in hormonal concentrations than in women on oral contraceptives who have a fairly stable sex hormonal milieu. A Case-control trial with Thirty women ages 18-35 volunteered for this study: 15 “non-users” (emenorrheic) and 15 “users” (taking oral contraceptives). The “Non-users” were tested in the follicular (lowest estrogen; days 1-3), peri-ovulatory (highest estrogen; days 12-14) and luteal phases (highest progesterone; days 20-24). “Users” were tested on corresponding days. Testing included serum hormonal analysis and HR testing (maximum H Reflex to maximum M-

wave ratio [Hmax/Mmax]) at three time points during the menstrual and contraceptive pill cycle. A series of 2 (Group: Users vs. NonUsers) x 3 (Time: menstrual and contraception cycle phase-Follicular, Ovulatory, and Luteal) mixed-model analyses of variance were conducted as the primary analyses. There were no significant differences between the groups with respect to age or body mass index. The H/M Ratio was lower in the "users" compared to the "non-users" in all phases, but the ANOVA examining H/M Ratio yielded no significant interaction, $F(2, 56) = 0.671$, $P = 0.515$, partial $\eta 2 = 0.023$ or main effects for group $F(1, 28) = 2.748$, $P = 0.109$, partial $\eta 2 = 0.089$ or phase in the cycle $F(1, 28) = 0.742$, $P = 0.481$, partial $\eta 2 = 0.026$. Our conclusion is that the basic neuromuscular control, as measured by the MSR, changes throughout the menstrual cycle. In this study, motor neuron excitability did not demonstrate a concordant change. Therefore, it is possible that the origin of hormonally-mediated changes in the MSR occurs in the connective tissue rather than the neural circuitry.

Disclosures: E.K. Casey: None. **M.E. Reese:** None. **E. Okafor:** None. **D. Chun:** None. **C. Gagnon:** None. **F.F. Nigl:** None. **Y.Y. Dhaher:** None.

Poster

606. Motoneuron Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 606.17/O7

Topic: D.13. Motor Neurons and Muscle

Support: NIH NINDS NS077863

NSF GRFP 2012137838

Title: Persistent Inward Currents of adult mouse spinal motoneurons, recorded *in vivo* using single electrode discontinuous voltage clamp (SEDVC)

Authors: *S. HUH[1], C. J. HECKMAN[2], M. MANUEL[3];
[2]Physiol., [1]Northwestern Univ., Chicago, IL; [3]Univ. Rene Descartes Paris, Paris, France

Abstract: Motoneurons possess a unique set of channels that generate a large persistent inward current (PIC). Because this current is activated near cell resting potential and inactivates very slowly, it plays a vital role in setting the intrinsic excitability of a MN as well as in amplifying synaptic inputs. To record PICs one needs to be able to control the voltage of the neuron, using SEDVC. Voltage clamp of adult spinal MNs have been performed in cats and larger rodents but has never been carried out in smaller rodents, such as mice, partially because of the difficulty of

the *in vivo* preparation necessary to keep adult spinal MNs viable. Thus, the goal of this study is to verify the role of PICs and their effect on MN firing patterns in adult mice. Not only do the sizes of MNs differ between cats and mice (mouse MNs are approximately half the size of cat MNs), some differences have already been observed in mouse motor unit firing patterns compared to cats. Unlike cat or rat motor units, mouse motor units require a wide firing range to accommodate the faster rate of muscle fiber contraction. Thus, mouse MNs have a faster membrane time constant, faster after hyperpolarization (AHP) and high frequency subthreshold oscillations at around 100-150 Hz that create a subprimary range (SPR) of firing where firing rate increases non-linearly with increasing current injection. Our preliminary data suggest there is a strong correlation between size of motoneurons (measured by input conductance) and current threshold to fire action potentials as well as voltage at which PICs activate and deactivate. Our data also show motoneurons that are able to fire repetitively have significantly larger PICs compared to ones that are not able to repetitively fire. In addition, motoneurons become larger with age, while PIC amplitude tends to decrease , resulting in a larger percentage of motoneurons from older animals that cannot repetitively fire. In Amyotrophic Lateral Sclerosis, exitotoxicity has been implicated in motoneuron degeneration, and this process could be exacerbated by increased PICs, we will therefore compare PIC amplitude in SOD1 and WT mice.

Disclosures: S. Huh: None. **C.J. Heckman:** None. **M. Manuel:** None.

Poster

606. Motoneuron Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 606.18/O8

Topic: D.13. Motor Neurons and Muscle

Support: Canadian Institutes of Health Research

Natural Sciences and Engineering Research Council

Alberta Innovates Health Solutions

Canada Foundation for Innovation

Women and Children's Health Research Institute

Title: Developmental modulation of persistent inward currents in XII MNs

Authors: *A. L. REVILL[1,2,3], N. Y. CHU[1], M. J. LEBLANCQ[3], C. T. DICKSON[3,4], G. D. FUNK[1,3,2];
[1]Dept. of Physiol., [2]Women and Children's Hlth. Res. Inst., [3]Neurosci. and Mental Hlth. Inst., [4]Dept. of Psychology, Univ. of Alberta, Edmonton, AB, Canada

Abstract: Hypoglossal (XII) motoneuron (MN) activity helps to maintain airway patency during wakefulness by preserving tone in the genioglossus muscle (GG), a tongue protruder. During REM sleep, however, atonia in the GG is implicated in obstructive sleep apnea. Thus, understanding the mechanisms that underlie the REM-sleep atonia of airway muscles is crucial. Active inhibition contributes in XII MNs, but the major mechanism appears to be disfacilitation; i.e., state-dependent loss of excitatory modulation, primarily α_1 noradrenergic and muscarinic, although serotonergic mechanisms also contribute. Over the first two postnatal weeks, 5-HT_{2A} receptor expression increases as does α_1-receptor mediated potentiation of XII inspiratory output. In spinal MNs, monoamines potentiate persistent inward currents (PICs), which are long-lasting, voltage-dependent Ca^{2+} and Na^{+} currents that increase excitability by amplifying synaptic inputs. Whether loss of modulatory tone and resultant reduction in PIC amplitude contributes to REM-sleep atonia is not known for any MN pool. The objectives of this study were to assess in XII MNs from neonatal (postnatal day, P1-4) and juvenile SD rats (P14-23), postnatal changes in PIC amplitude and sensitivity to α_1 noradrenergic, muscarinic and serotonergic modulation. Using whole-cell patch clamp techniques, we evoked PICs with slow voltage ramps (-80 to 0 to -80 mV, 5 to 14 mV/s) before and after bath application of 1 or 10 μM phenylephrine (PE, α_1-receptor agonist), 10 μM serotonin (5HT) or α-methyl-5HT, or 25 μM muscarine. PICs were evident in all MNs (neonates, n=28; juveniles, n=22) and there was a developmentally significant increase in baseline PIC amplitude from -195 ± 12 pA in neonatal to -342 ± 33 pA ($p < 0.05$) in juvenile MNs. As membrane capacitance does not change significantly over this time frame, postnatal increases in PIC amplitude represent an increase in PIC current density. PE and muscarine potentiated (>10%) PICs in a greater percentage of juvenile (PE: 86%, 6/7; muscarine: 50%, 6/12) than neonatal MNs (PE: 50%, 6/12; muscarine: 0%, 0/8). Serotonin potentiated PICs in 1/8 neonatal and 1/3 juvenile MNs. In sensitive neurons, the magnitude of PE potentiation did not change developmentally (16 ± 3% vs 19 ± 5%), but the efficacy of muscarine increased from -12% in neonates to 48% in juveniles. These data demonstrate that PIC current density, the number of MNs expressing a modulator-sensitive PIC and PIC sensitivity to muscarine increase postnatally. Measurements of MN properties during natural sleep will be required to fully address the functional significance of these observations. Supported by CIHR, NSERC, AIHS, CFI and WCHRI.

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Poster

606. Motoneuron Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 606.19/O9

Topic: D.13. Motor Neurons and Muscle

Support: CIHR FRN 79413

Title: Motoneuron excitability regulation changes during C-bouton development in mice

Authors: *I. PANEK[1], A. THANA[2], R. M. BROWNSTONE[2,3];
[2]Med. Neurosci., [3]Surgery (Neurosurgery), [1]Dalhousie Univ., Halifax, NS, Canada

Abstract: Modulation of motoneuron (MN) input-output gain is a key mechanism implicated in generating appropriate motor output. Cholinergic C-bouton synapses play an essential role in regulating MN excitability. Previous anatomical studies suggest that C-boutons undergo postnatal maturation, which involves clustering of delayed rectifier Kv2.1 channels, small-conductance Ca2+-gated K+-channels (SK2 & SK3) and type 2 muscarinic receptors (M2R) at the postsynaptic site. Whether this anatomical clustering relates to physiological properties is not known. Using patch-clamp recordings in spinal cord slice, we describe the electrophysiological properties of immature (P3) and adult (P20+) mouse MNs. We show that the SK channel blocker apamin (100nM) produces a smaller increase in excitability in neonatal than adult MNs (f-I slope increase of 238 ± 101% vs. 544 ± 464% in adult MNs). Correspondingly, activation of M2Rs by muscarine (50μM) application has minimal effect on the input-output gain of neonatal MNs, but increases the frequency-current slope by 80% in adult MNs. That is, we have demonstrated that physiological maturity occurs at the time of clustering of channels at the post-synaptic membrane. We hypothesize that channel clustering is needed for functional cooperation between these C-bouton elements. For example, M2Rs and SK channels may need to reside close together in order to exert a full range of modulatory effects.

Disclosures: I. Panek: None. **A. Thana:** None. **R.M. Brownstone:** None.

Poster

606. Motoneuron Excitability

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 606.20/O10

Topic: D.13. Motor Neurons and Muscle

Title: Transient receptor potential vanilloid 1 (TRPV1) and transient receptor potential ankyrin-1 (TRPA1) activators reduce muscle cramping

Authors: *G. SHORT, B. W. HEGARTY, C. H. WESTPHAL, J. M. CERMAK;
Flex Pharma Inc, Boston, MA

Abstract: Muscle cramps can be painful and debilitating, for healthy athletes as well as patients suffering from nocturnal leg cramps, multiple sclerosis, amyotrophic lateral sclerosis, and other neurological diseases. Flex Pharma is developing treatments for neuromuscular disorders including muscle cramps and spasms. Recent studies have demonstrated that hyperexcitability of α-motor neurons in the spinal cord is likely the underlying cause of cramps and spasticity. Based on a general property of neuronal circuits, whereby strong excitatory input increases inhibitory tone and reduces responsiveness to excitation, we hypothesized that transient receptor potential channel (TRP) activation could yield sufficient excitatory input to dampen motor neuron hyperexcitability. To test this hypothesis, we conducted human studies to assess the effectiveness of TRP activation in inhibiting electrically-induced cramps of the foot. An oral solution containing a mixture of TRP activators derived from natural extracts was shown to prevent cramps within minutes of ingestion, lasting up to 6-8 hours. The aggregated results from three independent, randomized, blinded clinical studies showed a significant reduction in cramp intensity by 3-fold ($p<0.0001$). Review of EMG output showed that cramps were reproducibly elicited with little intra-subject variation for threshold settings and cramp profile. However, EMG patterns varied considerably between subjects. Cramp profiles (area under the curve for cramp intensity and duration) fell under several sub-types: 1) low intensity but sustained for several minutes on EMG, 2) high intensity with a rapid return to baseline, 3) delayed onset, 4) high intensity and sustained, and 5) multi-phasic sustained. Most subjects fell into subtype 1. Interestingly, pain related to cramp induction often subsided well before resolution of cramp by EMG. There was no difference between the threshold settings to induce cramp and cramp profile. The Flex proprietary formulation was effective at reducing cramp intensity across all cramp subtypes. The results demonstrate that TRP activators may be an effective new treatment in individuals suffering from cramps and spasms. Flex Pharma has initiated a study in nocturnal leg cramps and may initiate studies in multiple sclerosis, and other neurologic disorders, in addition to studies in healthy athletes.

Disclosures: **G. Short:** A. Employment/Salary (full or part-time):; Flex Pharma Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Flex Pharma Inc. **B.W. Hegarty:** A. Employment/Salary (full or part-time):; Flex Pharma Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Flex Pharma Inc. **C.H. Westphal:** A. Employment/Salary (full or part-time):; Flex Pharma Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property

rights/patent holder, excluding diversified mutual funds); Flex Pharma Inc. **J.M. Cermak:** A. Employment/Salary (full or part-time):; Flex Pharma Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Flex Pharma Inc.

Poster

607. Motoneuron Excitability: Afferent Input

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 607.01/O11

Topic: D.13. Motor Neurons and Muscle

Support: Swedish Research Council

Ragnar Söderberg Foundation

Karolinska Institutet

Knut and Alice Wallenberg Foundation

Swedish Brain Foundation

Title: Genetic tools to study sensory motor circuits

Authors: *A. SHARMA[1], H. WU[1], C. BELLARDITA[2], Y. XUAN[1], K. MELETIS[1], O. KIEHN[2], F. LALLEMEND[1];
[1]Dept. of Neurosci., [2]Mammalian Locomotor Laboratory, Dept. of Neurosci., Karolinska Institutet, Stockholm, Sweden

Abstract: Sensory feedback from skeletal muscles is essential for fine, coordinated motor control. The gatekeepers of this feedback are the proprioceptive sensory neurons (PSNs) whose cell bodies are in the dorsal root ganglia (DRG), and are classified into three subtypes (Ia, Ib, and II) depending on their anatomy and physiology. Currently only electrophysiology allows precise discrimination between the different subtypes of PSNs, critically hindering investigations into these important cells and the networks of which they are a part. Here we address this problem, uncovering the genetic identity of the PSN subtypes in mice, with an initial focus on Ia PSNs, using a powerful combination of mouse genetics, rabies virus mediated retrograde tracing and single cell transcriptomics. Our first approach consists of classifying PSNs subtypes by single cell RNA-seq analysis of hundreds of genetically labelled parvalbumin (PV) positive PSNs in mice of different ages. In our second approach, we employ monosynaptic tracing from motor

neurons in the spinal cord by injection of modified rabies virus in the ventral horn of the spinal cord of mice, specifically retrogradely labelling Ia PSNs in the DRGs. These specifically labelled Ia PSNs are then analysed by single cell RNA-seq, revealing for the first time the genetic identity of the Ia PSNs. We are currently validating our single cell data and are comparing them to the transcriptome profile of non-PSN DRG and spinal cord cells in order to define specific genetic markers of Ia PSNs. Our final aim is to produce knock-in mouse lines to allow fast and accurate *in vivo* and *in vitro* labelling and manipulation of Ia PSNs.

Disclosures: **A. Sharma:** None. **H. Wu:** None. **C. Bellardita:** None. **Y. Xuan:** None. **K. Meletis:** None. **O. Kiehn:** None. **F. Lallemend:** None.

Poster

607. Motoneuron Excitability: Afferent Input

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 607.02/O12

Topic: D.13. Motor Neurons and Muscle

Support: National Institute of Health Research Senior Clinical Lectureship

Title: The effect of joint flexibility and knee pain upon corticospinal and reflex control of quadriceps

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Abstract: Joint Hypermobility Syndrome (JHS) is characterised by overly flexible joints alongside symptoms[1]. Symptoms range from longstanding multi-joint pain, joint instability, soft-tissue injury and skin abnormalities[1] as well as muscle weakness[2]. It is unclear why some flexible people have symptoms and some do not however, it may be due to impaired mechanisms of control[4]. Surprisingly, mechanisms of control comparing overly flexible people with and without pain and the normally flexible have not been thoroughly investigated; this is the aim of the study. With ethical approval and informed consent, 55 age-matched people were recruited. As pain is most severely but not exclusively felt in the knees of people with JHS[3], the following cohorts were recruited; people with JHS and knee pain (Beighton=7/9±2, n=15), people with JHS without knee pain (Beighton=6/9±2, n=20) and people with normal flexibility (Beighton=1/9±1, n=20). JHS and pain were classified using Brighton Criteria[1], pain mapping and visual analogue scales respectively. Transcranial magnetic stimulation was delivered over

the hotspot for the quadriceps motor cortex using a figure of eight coil and the stimulus intensity was incrementally increased. Electromyographic activity was recorded from the quadriceps of the dominant leg[5] in asymptomatic knees or the most painful side. Separately, the femoral nerve was stimulated incrementally over the skin within the femoral triangle to evoke the Motor (M) response and Hoffman (H) reflex. Outcomes measured were MEP threshold, latency, slope of the MEP recruitment curve where MEPs were normalised to Mmax and the MEPmax/Mmax. In addition, the slope of the ascending limb of the normalised H-reflex recruitment curve and Hmax/Mmax were recorded. MEP Threshold, latency, MEPmax/Mmax, H-reflex slope and Hmax/Mmax were no different across the three cohorts however; MEP slope was steeper in people with JHS and knee pain compared to people with JHS without pain and people with normal flexibility (0.02±0.01, 0.01±0.01, 0.01±0.01 respectively; p=0.03). One interpretation is that people with JHS and knee pain are compensating for their lack of strength by modulating corticospinal recruitment. It seems that pain is a critical factor rather than the degree of flexibility as people with JHS without knee pain are no different to the normally flexible. 1 Grahame R et al. J Rheumatol 2000 27(7):1777-9. 2 Sahin N et al. Rheumatol Int 2008 28(7):643-8. 3 Booshanam DS et al. Rheumatol Int 2010 May 20. 4 Rombaut L et al. Arthritis Care Res (Hoboken) 2012 64(10):1584-92. 5 Vauhnik R et al. Knee Surg Sports Traumatol Arthrosc 2008 16(9):823-33.

Disclosures: **C.M. Alexander:** A. Employment/Salary (full or part-time):; National Institute of Health Research. **J. Kassam:** None. **M. Long:** A. Employment/Salary (full or part-time):; Imperial College London. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Imperial College Healthcare Charity.

Poster

607. Motoneuron Excitability: Afferent Input

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 607.03/O13

Topic: D.13. Motor Neurons and Muscle

Support: BBSRC

Title: An optogenetic approach to understanding fine control of fast locomotion

Authors: ***O. CAPPELLARI**[1], K. E. WELLS[1], S. D. WILSHIN[2], J. CHARLES[1], J. R. HUTCHINSON[2], A. J. SPENCE[3], D. J. WELLS[1];

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Abstract: Optogenetics refers to the use of light to activate or inactivate excitable tissues that have been genetically modified with light-sensitive proteins (opsins). Despite widespread use in basic neuroscience and in application to neurological disorders, optogenetics has not been extensively used to study locomotion, and especially fast locomotion, for which it's high temporal resolution is ideally suited. Moreover there are not many studies with optogenetics applied in the periphery. This project aims to use optogenetics to dissect the coupled interaction of the nervous system, musculoskeletal system, and physics of the moving body. Using these tools it is becoming possible to precisely perturb specific neuronal pathways during locomotion in freely running animals. Here we present work seeking to specifically activate muscles on one hand, meanwhile on the other hand silence sensory feedback, in freely moving mice. The scientific goal accompanying the former technological aim is to understand how gait control is regulated in the presence of perturbations, without causing spurious sensory feedback (as would result from electrical nerve stimulation) through optical stimulation of motor neurons in the sciatic. The mouse model being used for this aim is a ChAT-Chr2-EYFP transgenic (Zhao et al., Nat Methods. 2011, 8(9):745-52.) which has the optical activator channelrhodopsin driven by the mouse choline acetyltransferase promoter, which in the periphery is exclusively expressed in motor neurons. An optical implantable microLED cuff has been built in order to stimulate the opsin solely at the level of the sciatic nerve. This mouse has also helped us to identify some limitations of optogenetics when used in the peripheral nervous system, as compared to the central nervous system. The selected line demonstrated severe developmental issues including delayed growth and impaired locomotion. We partially correct these issues by outbreeding the mouse line on a different genetic background. Moreover an interesting muscle fiber typing shift has been observed. We also noted that mouse to mouse anatomical variation in motor neuron distribution modulates the response to optogenetic stimulation. To achieve the second aim of sensory silencing, a second mouse model is currently under construction in which the neuronal silencer halorhodopsin is expressed under the control of a muscle spindle specific promoter, which represents a major component of the proprioceptive feedback in locomotion. Finally by crossing these two mice we will be able to both stimulate muscle activity and dampen feedback in the same mouse, in order to dissect the neuromechanical basis of locomotion.

Disclosures: O. Cappellari: None. **K.E. Wells:** None. **S.D. Wilshin:** None. **J. Charles:** None. **J.R. Hutchinson:** None. **A.J. Spence:** None. **D.J. Wells:** None.

Poster

607. Motoneuron Excitability: Afferent Input

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 607.04/O14

Topic: D.13. Motor Neurons and Muscle

Support: MEXT23592750

MEXT25350622

Title: Presynaptic histaminergic inhibition of synaptic transmission from mesencephalic trigeminal afferents to masseter motoneurons in juvenile rats

Authors: *K. NAKAYAMA[1], C. GEMBA[2], S. NAKAMURA[1], A. MOCHIZUKI[1], M. INOUE[2], T. INOUE[1];
[1]Dept. of Physiol., [2]Dept. of Pediatric Dent., Showa Univ. Sch. of Dent., Tokyo, Japan

Abstract: Histamine receptors are densely expressed in brain regions that control oral-motor activity such as mesencephalic trigeminal sensory nucleus (MesV) and trigeminal motor nucleus. Previously, we have reported that histamine reduces the peak amplitude of the postsynaptic currents (PSCs) in the masseter motoneurons (MMNs) evoked by electrical stimulation of the trigeminal nerve tract (5N), which includes MesV afferents from the jaw-closing muscles and the periodontal ligaments. In the present study, we examined the mechanisms of histaminergic modulation of the 5N stimulation evoked-PSCs in MMNs using whole cell patch-clamp recording technique in brainstem slice preparations from Wister rats aged between postnatal days 7 and 13. To block antidromic activation of MMNs by 5N stimulation, 5 mM lidocaine *N*-ethyl bromide (QX-314) was added to the pipette solution. The inhibition of the 5N stimulation-evoked PSCs by histamine was mimicked by 100 μM 2-pyridylethylamine dihydrochloride, an H1 receptor agonist. Bath-application of 2-pyridylethylamine reduced the peak amplitude of the evoked PSCs by 47 ± 6.3% (n = 7). The inhibition of the evoked PSCs by 2-pyridylethylamine and histamine was blocked by 10 μM triprolidine hydrochloride, an H1 receptor antagonist. In contrast, 100 μM dimaprit dihydrochloride, an H2 receptor agonist, and 100 μM immethridine dihydrobromide, an H3 receptor agonist, produced little effect on the peak amplitude of the evoked PSCs. These results suggest that histaminergic inputs via H1 receptors likely inhibit the PSCs evoked by stimulation of the MesV afferents. Next, we investigated the effects of 2-pyridylethylamine on monosynaptic PSCs in MMNs evoked by 5N minimal stimulation at an intensity just above the threshold. Bath application of 100 μM of 2-pyridylethylamine significantly increased the failure rate of the monosynaptic PSCs by 101 ± 20% (n = 7, P = 0.010), although the differences in mean peak amplitudes were not significant (P = 0.086). Such increase in the failure rate was antagonized by triprolidine. Subsequently, we studied the effects of 2-pyridylethylamine on the paired-pulse ratios (PPRs) of the evoked PSCs in MMNs. Bath application of 2-pyridylethylamine increased the PPRs significantly (n = 9, P = 0.001) and the increase in the PPRs by 2-pyridylethylamine was antagonized by triprolidine. These results

suggest that a presynaptic mechanism via H1 receptors is involved in the histaminergic inhibition of synaptic responses to MMNs from MesV afferents.

Disclosures: K. Nakayama: None. **C. Gemba:** None. **S. Nakamura:** None. **A. Mochizuki:** None. **M. Inoue:** None. **T. Inoue:** None.

Poster

607. Motoneuron Excitability: Afferent Input

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Topic: D.13. Motor Neurons and Muscle

Support: EU-FP7-ICT-2011-287739

EU-FP7-PEOPLE-2013-IOF-627384

Title: Shared synaptic input to motoneuron pools from different limbs in essential tremor

Authors: *J. GALLEGO[1], J. L. DIDERIKSEN[2], A. HOLOBAR[3], J. L. PONS[4], E. ROCON[5], D. FARINA[6];
[1]Dept. of Physiol., Northwestern Univ., Chicago, IL; [2]Aalborg Univ., Aalborg, Denmark; [3]Univ. of Maribor, Maribor, Slovenia; [4]Spanish Natl. Res. Council, Madrid, Spain; [5]Spanish Natl. Res. Council, Arganda del Rey, Spain; [6]Georg-August Univ., Göttingen, Germany

Abstract: Essential tremor (ET) manifests as a bilateral tremor of the hands. Imaging and electrophysiological studies suggest that ET originates from pathological oscillatory activity in the cerebello-thalamo-cortical pathways. The projection of this oscillatory activity to motoneurons innervating the affected muscles ultimately generates the tremulous movement. Previous studies examining “inter-limb coupling” in ET patients indicated that the tremor in different arms originates from different brain sites, based on the lack of significant coherence between their rectified EMGs. This was interpreted as implying the existence of multiple somatotopically organized pathological oscillatory circuits in the brain. We investigated, using direct measures of common input to motoneurons, whether muscles in different limbs receive a common tremor synaptic input. We recorded multichannel EMGs from the wrist extensors and flexors of 14 ET patients bilaterally, while they performed a postural task. We decomposed those signals into motor unit spike trains using the convolution kernel compensation algorithm, and characterized the neural drive to each of this four muscles as the composite spike trains (sum) of all the identified motor units. The average number of accurately detected motor units per muscle

was 7.5 ± 4.6. In four patients, the motoneuron pools from different arms received the same common tremor synaptic input, as revealed by the analysis of coherence between their composite spike trains. For the other ten, we did not find significant inter-limb coupling. In the patients with tremor inputs shared across limbs, one pair of neural drives was synchronized, according to the analysis of phase difference using the Hilbert transform. This indicates that motoneuron pools from different arms received the same supraspinal tremor drive. The tremor frequency was not identical across limbs, which suggests an effect of spinal and/or mechanical factors. In addition to the shared tremor drive, we found a bilaterally shared common voluntary input in 28 of the 45 examined pairs of motoneuron pools (six of them along with the shared tremor drive), suggestive of shared supraspinal control. We argue that a single central oscillator may be causative of the bilateral tremor in some ET patients, and that the pathophysiology of ET is widely dissimilar across individuals.

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Poster

607. Motoneuron Excitability: Afferent Input

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 607.06/O16

Topic: D.13. Motor Neurons and Muscle

Title: Topographical distribution of corticospinal axons in the mouse spinal cord

Authors: *H. KAMEDA[1], N. MURABE[1], H. MIZUKAMI[2], K. OZAWA[2], M. SAKURAI[1]; [1]Teikyo Univ. Sch. of Med., Tokyo, Japan; [2]Jichi Med. Univ., Tochigi, Japan

Abstract: The corticospinal (CS) tract is essential for voluntary movement. Despite numerous studies, what we know about CS tract organization remains limited. Our previous study using retrograde tracers showed that CS neurons projecting to the 7th cervical cord (C7) distributed not only in the primary motor cortex (M1), but also in the primary (S1), secondary somatosensory (S2) and secondary motor cortices (M2), which is also referred to as rostral forelimb area (RFA) in the recent literature. There are several studies about projection of M1 and S1 CS neurons in rodents: M1 CS neurons send their axons mainly to the ventral part of the spinal cord, where motoneurons are located, and S1 to the dorsal part, which receives sensory inputs. These results imply that M1 CS neurons are related more directly to movements, and S1 to modulation of sensory processing. However, the comprehensive study of the CS neurons located in the other motor-related cortices is lacking and the role of these neurons is still unknown. In the present

study, to investigate the axonal distribution of CS neurons located in the other areas, we first injected adeno-associated virus (AAV) serotype 1 vectors expressing fluorescent proteins of different colors, which were fused with channelrhodopsin-2 (ChR2-XFPs) into the cortical areas separately at P56. ChR2-XFPs labeled axons clearly without gaps down to their terminals because ChR2 is the transmembrane protein, and the tagged XFPs are located just beneath the plasma membranes of axons. The mice were fixed two or three weeks after viral injections. We analyzed the axonal distribution in the C7 and found that CS neurons were divided into three groups according to the innervating area in the spinal cord: (1) CS axons from RFA and M1 were mainly distributed in the intermediate and ventral parts, (2) rostral part of S1 projected mainly to the mediodorsal part, (3) caudal part of S1 and S2 to dorsolateral part. There was almost no overlap in innervating areas, raising the possibility that these projection systems play separate roles. Double immunostaining of XFP-positive CS axons and NeuN revealed that the axons from RFA and M1 distributed mainly at inner lamina V to lamina VII, and those from S1 and S2 at lamina III to outer lamina V. We also investigated the axonal distribution of the three groups at other spinal segments and found that the similar topography was observed in the C5 and first thoracic cord. We further injected AAV into the several parts of cortical hindlimb area and found that the rostromedial part projected mainly to the intermediate and ventral parts, and caudolateral part to the dorsal part in the L4.

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Poster

607. Motoneuron Excitability: Afferent Input

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Topic: D.13. Motor Neurons and Muscle

Support: NWO-ALW grant 864-10-011

NIH-NINDS grant PO1-NS057228

Title: Epimuscular myofascial loads affect tendon organ firing behavior

Authors: *H. A. SMILDE[1,2], J. A. VINCENT[2], G. C. BAAN[1], P. NARDELLI[2], T. C. COPE[2], H. MAAS[1];
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Abstract: Skeletal muscles are not exclusively connected to bone via their tendons, but also via connective tissues to neighboring muscles. Via such epimuscular myofascial connections length changes of a muscle can cause local force differences within an adjacent muscle. Our aim was to investigate myofascial effects on feedback from tendon organs. We hypothesized that output from tendon organs can be affected by length changes of adjacent muscles and that these effect are dependent on tendon organ location. In fully anesthetized female Wistar rats (n=7), the distal tendon of soleus (SO) and those of gastrocnemius and plantaris (GAS+PL) were attached to servo motors, which controlled muscle-tendon unit length and measured tendon force. Reference length (Lref) corresponded to ankle and knee angle at 90°. Connective tissues at the muscle belly level were left intact. Action potentials from single afferents were measured intra-axonally in response to ramp stretches of the agonistic muscle for different lengths of its synergist. Firing responses of an afferent located within one muscle were measured also during ramp stretches of its synergist. The muscle surface was probed to localize the afferent. The following parameters were assessed: length and force at the occurrence of the first action potential (thresholds), instantaneous firing rate (IFR) at peak of the ramp and halfway through the hold phase, the difference between these parameters (dynamic index, DI), and the rate of change in IFR during the ramp (ramp slope). SO (n=10): Lengthening GAS+PL from Lref-2 to Lref+4 mm decreased force threshold ($p=0.020$) from 0.37 N to 0.21 N, despite an equal ramp stretch to SO. Also DI decreased from 45 to 34 pps ($p=0.011$). Length threshold, IFR peak ramp, IFR half hold and ramp slope were also affected in most afferents, but in various directions. All SO tendon organs responded to a ramp stretch of GAS+PL. LG (n=14): Lengthening SO decreased IFR peak ramp ($p<0.001$, from 111 to 88 pps), IFR half hold ($p=0.016$, from 50 to 42 pps) and DI ($p=0.014$, from 60 to 46 pps) of LG tendon organs. The length threshold increased ($p=0.003$) with 0.46 mm; length threshold at Lref=1.04 mm. The changes in force threshold and ramp slope varied between afferents. Twelve LG afferents fired in response to a SO ramp stretch. These results indicate that feedback from tendon organs of an agonist can be affected by length changes of synergistic muscles. Although the individual differences could not directly be linked to the location of afferents within the muscle belly, such differences are in agreement with our hypothesis that tendon organs in different locations are affected differently by myofascial loads.

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Poster

607. Motoneuron Excitability: Afferent Input

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Topic: D.13. Motor Neurons and Muscle

Support: LO591506

LM207849

PIFI2013

C-703/2013UV

Title: Reflex activity of pubococcygeus muscle motoneurons by clitoris stimulation in the rat

Authors: *O. LARA GARCIA[1], D. PÉREZ GARCÍA[2], M. MARTINEZ GOMEZ[3,4], M. LARA GARCIA[4], P. PACHECO[3,2];
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Abstract: We have described that pubococcygeus muscle (Pcm) of the female rat, which participates in reproductive processes (copulation, delivery) as well as in micturition, responds to clitoris stimulation depending to gonadal hormonal levels. It has been proposed that spinal cord interneurons participate in the response of its motoneurons. In order to further analyze this response we used electrical stimulation to the dorsal nerve of the clitoris (DNC). Bilateral EMG recordings were obtained using bipolar stainless steel electrodes (0.1mm) by clitoris and vagina-cervix-uterus junction (VCUJ) pressure, and electrical pulses to the DNC. Phasic and tonic on-off activity was recorded during clitoris pressure. The VCUJ stimulation blocks both tonic and phasic responses. A single pulse to the DNC produce ipsilateral electromyographic Pcm potentials with 10 msec of latency; trains of 10 per second produce ipsilateral tonic on responses and bilateral tonic off responses, but phasic responses. Our results suggest that the tonic on motoneuronal discharge is ipsilateral while tonic off is bilaterally activated. According to the EMG latency (15msec) of the evoked potential response obtained during the electrical stimulation of the DNC, A β afferent and efferent transmission (0.7msec each), neuromuscular junction delay (1.2msec) and 6 interneuronal synapses delay (approx. 1.2 msec each) are involved in the clitoris-Pcm reflex. Genital tactile stimulation including the clitoris in women is regarded as a precursor to sexual arousal, effect that is claimed beginning at the receptors level and following a course through the central nervous system (CNS). However, there is not information regarding the physiological connections of the clitoris with pelvic floor musculature, notwithstanding that Kegel´s exercises could be involved in this connection. Moreover, it is known that gonadal hormones variations affect synaptic strength at neuromuscular junction in striated muscles related to reproduction; therefore, Pcm activity besides of its relation with reproductive processes is highly involved in sexual responses, such as orgasm.

Disclosures: **O. Lara Garcia:** None. **D. Pérez García:** None. **M. Martinez Gomez:** None. **M. Lara Garcia:** None. **P. Pacheco:** None.

Poster

607. Motoneuron Excitability: Afferent Input

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Topic: D.13. Motor Neurons and Muscle

Support: NWO-ALW Grant 864-10-011

Title: Enhanced muscle connectivity changes neural control of synergistic muscles during locomotion

Authors: ***M. BERNABEI**, J. H. VAN DIEËN, H. MAAS;
Human Movement Sci., MOVE Res. Inst. Amsterdam, Amsterdam, Netherlands

Abstract: Altered intermuscular connectivity, associated with neuromuscular diseases, muscle injury and reconstructive surgery, has been found to affect force transmission between individual muscles within a synergistic group. To date, it is unknown whether the neural control of synergistic muscles adapts to such changes in muscle connectivity. Therefore, the aim of this study was to investigate effects of enhanced connectivity between ankle plantar-flexors on muscle activity patterns during locomotion. Wistar rats (n=3), trained for trotting on a treadmill, were instrumented with electromyographic (EMG) electrodes in soleus (SO) and lateral gastrocnemius (LG). After recording baseline EMG activity and hindlimb kinematics, the stiffness of intermuscular connective tissues was increased by implanting a tissue-integrating mesh between SO and LG (n=2). Three weeks post surgery, the root-mean-square (RMS) of SO EMG was decreased by 38.5% and 61.6% ($p<.001$), while RMS of LG was increased by 125.8% and 187.2% ($p<.001$) in the rats with increased connectivity. While at baseline EMG activity of SO was higher than that of LG, increased intermuscular connectivity caused a reversal of this pattern to preferential recruitment of LG. Ranges of motion for hip, knee and ankle joints were within two standard deviations from baseline values, while stride length and duration appeared to deviate from baseline, but with opposite trends between rats. No significant changes in hindlimb kinematics, RMS values or recruitment patterns were found in the control animal over the same measurement period. Enhanced mechanical coupling between SO and LG yielded substantial changes in the magnitude and coordination of plantar-flexor activity. Possibly the reduction of mechanical degrees of freedom is sensed by the central nervous system (CNS), as the mechanical effects of SO and LG activation around ankle and knee joints may become more similar.

Consequently a loss of muscle recruitment selectivity could evolve as an adaptation to the peripheral changes. Alternatively, given the difference between SO and LG in cross-sectional area and fiber type composition, maintenance of the functional output with a loss of torque capacity may require the CNS to change the contribution of the two synergists. These results may have implications for surgery involving connective tissue disruption and for pathological conditions, such as stroke and cerebral palsy, often associated with abnormal connective tissues.

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Poster

607. Motoneuron Excitability: Afferent Input

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Topic: D.13. Motor Neurons and Muscle

Support: NINDS PO1NS057228

Title: The severity of the central neuroimmune response following peripheral nerve injury correlates with the amount of proprioceptive IA afferent loss from injured motoneurons

Authors: *T. M. ROTTERMAN, F. J. ALVAREZ;
Physiol., Emory Univ., Atlanta, GA

Abstract: Following peripheral nerve injury there is a central immune response in which native microglia cells and infiltrating peripheral macrophages surround injured motoneurons (MNs). In parallel, proprioceptive IA afferent synapses are permanently deleted from MNs, which ultimately results in persistent motor deficits. We hypothesized that 1) a sciatic (proximal) nerve transection will result in an enhanced immune response compared to a tibial (distal) nerve injury and 2) an enhanced immune response will correlate with a larger depletion in IA afferent synaptic inputs. To test these hypotheses we used dual heterozygous "knock-in" CX_3CR1 (EGFP/+) and CCR2 (RFP/+) transgenic C57Blk/6 mice to respectively label microglia (EGFP) and infiltrating peripheral macrophages (RFP). In these mice we retrogradely labeled lateral gastrocnemius MNs with Fast Blue, and this was followed by a second surgery in which either a sham, tibial, or sciatic nerve transection was performed. Fourteen days (before muscle reinnervation) or 2 months (after muscle reinnervation) following the injury we immuno-labeled for vesicular glutamate 1 transporter (VGLUT1), a marker of IA afferents. Labeled MN somas were imaged using confocal microscopy and reconstructed in 3D using the Neurolucida software to map their VGLUT1+ synapses. In addition, microglia and macrophages were quantified in a

volume of $2.2x10^6$ μm^3 (50 μm tissue section thickness) around labeled MNs using Imaris software. Fourteen days after injury the number of EGFP+ cells increased by 177% in the tibial nerve injury model and 347% after sciatic nerve injury compared to sham operated animals. Two months after injury the microglia reaction decreased and the number of microglia cells were now increased to only around 23% and 65% of controls. In contrast, there were no significant numbers of RFP+ cells in the ventral horn of sham operated animals, these cells were recruited after injury, and we detected 5 times more RFP+ cells 14 days after injury in sciatic transections compared to tibial nerve injuries. Similar to microglia the numbers of RFP+ cells diminished 2 months after injury. The density of VGLUT1 synapses on the cell bodies of injured MNs partially decrease after tibial nerve injury by 37% 14 days after injury and remained similarly depleted (26% decrease) after 2 months and muscle reinnervation. This depletion was much larger after sciatic nerve injury: 60% depletion 14 days after injury and 77% depletion at 2 months after. Taken together, our data indicates that a sciatic nerve transection induces a larger immune response that correlates with a larger depletion in somatic VGLUT1 synapses compared to a tibial nerve injury.

Disclosures: T.M. Rotterman: None. **F.J. Alvarez:** None.

Poster

607. Motoneuron Excitability: Afferent Input

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: D.13. Motor Neurons and Muscle

Support: KAKENHI 25350621

Title: The property of Ia excitation and recurrent inhibition of abdominal motoneurons in the cat

Authors: *M. NIWA[1], N. MUTO[2], S.-I. SASAKI[3];
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Abstract: The abdominal (Abd) muscles have divergent functions such as respiration, postural control, vomiting and defecation. However, it is not well known about reflex actions exerted on Abd motoneurons. The present experiments were undertaken to investigate how reflex actions exerted on the motoneurons work and whether recurrent inhibitory pathways are present in Abd motoneurons. Experiments were performed on adult cats anesthetized with sodium pentobarbital. The bipolar cuff electrodes were put in Abd nerves for electrical stimulation. The spinal cord was

exposed by a laminectomy. To eliminate descending supraspinal input, the spinal cord was transected at the junction of T12/T13. Animals were immobilized and maintained on artificial ventilation. Intracellular recording was made from Abd motoneurons (external oblique, internal oblique, transversus abdominis and rectus abdominis) to record antidromic spikes and excitatory post synaptic potentials (EPSPs) following stimulation relevant peripheral Abd nerves. All the experimental procedures were approved by the Animal Ethics Committee of Ibaraki Prefectural University of Health Sciences. The preparation of dorsal roots were as follows: 1)Dorsal roots were intact and muscle nerves electrically stimulated to activate Ia afferents. Ia-EPSPs elicited were found in almost all motoneurones following the stimulation of the homogeneous nerve in the same spinal segment. They are responsible for the monosynaptic EPSP of motoneurones of their muscles, although these values are longer than those values of the hind limb and the intercostals muscles. It suggests that the extent of Ia-EPSP of Abd motoneurones seem to be limited in the same spinal segment and the homogeneous motoneurone. 2) Dorsal roots were sectioned and muscle nerves were electrically stimulated to activate motor axons. Recurrent inhibitory post synaptic potentials (RIPSPs) elicited were found in approximately one quarter of abdominal motoneurons with an intensity subthreshold activation for axon of the impaled motoneuron. It is likely that abdominal motoneurons has few recurrent inhibitions, although it may be underestimated due to the stimulus condition of peripheral nerves. The present results provide evidence of Ia excitation and recurrent inhibition of abdominal motor nucleus. These neuronal circuits might be related to the control of abdominal muscles during various motor activities.

Disclosures: **M. Niwa:** None. **N. Muto:** None. **S. Sasaki:** None.

Poster

607. Motoneuron Excitability: Afferent Input

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 607.12/O22

Topic: D.13. Motor Neurons and Muscle

Support: grant support from Scottish Government Health Directorates

Title: Spinal direct current stimulation enhances vertical jump power in healthy adults

Authors: *H. R. BERRY[1], B. A. CONWAY[2];
[2]Biomed. Engin., [1]Strathclyde Univ., Glasgow, United Kingdom

Abstract: Transcutaneous spinal direct current stimulation (tsDCS) is a safe, non-invasive neuromodulation tool that can affect sensory, motor and pain spinal cord circuits and pathways. The polarity dependent neuroplastic effects are reported to persist after stimulation in a dose dependent manner. It is not known whether tsDCS neuromodulation can translate to any measurable change in functional motor power production post stimulation. In this study we investigate the effect of 15 min of anodal lumbosacral cord level tsDCS on vertical countermovement jump (VCJ) power production up to 3 hours after stimulation in healthy volunteers: the VCJ is a test of maximal lower limb power and involves a powerful eccentric countermovement. In tandem with this, we mapped concomitant changes in lower limb posterior root-muscle (PRM) reflexes over the same time course. We employed a double-blind, randomized, crossover sham-controlled design approved by our local ethics committee. 13 healthy individuals completed 5 maximal effort VCJs on a force platform before and 0, 20, 60 and 180 min after sham and active tsDCS (25 VCJs per session, at least 7 days apart). 6 of the subjects completed 2 further sham/active tsDCS session where lower limb PRM reflexes were induced before and up to 180 min after tsDCS using single pulse biphasic stimulation of the spine via the same electrode montage as in place for tsDCS. tsDCS induced a mean (95% CI) 15.4 (7.4_23.5)% difference in max (sham - 6.4%, active + 9%, $p < 0.001$) and a 11.4 (5_17.8)% difference in ave (sham - 5%, active + 6.4%, $p < 0.001$) countermovement power, leading to an overall difference of 4.2 (2.1_6.4)% in max (sham -3.6%, active +0.6%, $p < 0.001$) and 3.7 (1.9_5.6)% difference in ave peak to peak VCJ power (sham -2.7%, active +1%, $p < 0.001$). These changes did not significantly differ between time point post tsDCS. We found that over both tsDCS conditions, changes in hamstring PRM reflexes were positively correlated with changes in ave VCJ force ($r = 0.60$, $p < 0.001$). Anodal tsDCS preserved and enhanced countermovement power production over three hours, whereas there was a significant fatigue effect after sham tsDCS. These changes appear to be due to changes in force potentiation mechanisms, demonstrated by excitability changes in reflex circuitry. We have shown for the first time that anodal tsDCS quickly, easily and painlessly counters the fatigue normally associated with repeated maximal power performance. tsDCS-induced fatigue resistance and an enhancement of motor power in the absence of physical training have important implications for rehabilitation after central nervous system injury.

Disclosures: H.R. Berry: None. **B.A. Conway:** None.

Poster

607. Motoneuron Excitability: Afferent Input

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 607.13/O23

Topic: D.13. Motor Neurons and Muscle

Support: NSF Grant IOS 1120291

Brains & Fellowship from Georgia state University

Title: Reorganization of locomotor bursts by proprioceptive feedback

Authors: *J. BACQUE-CAZENAVE[1], B. CHUNG[1], D. CATTAERT[2], W. HEITLER[3], D. H. EDWARDS[1];
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Abstract: During walking in crayfish, leg Depressor (Dep) and Levator (Lev) muscles are active and the coxobasal chordotonal organ (CBCO) provides proprioceptive feedback to the thoracic nervous system. We found that CBCO feedback in closed loop accelerates the walking rhythm and organizes motor bursts. The CBCO is a stretch receptor that codes up and down movement around one crayfish leg joint. Activity of the CBCO nerve and Dep and Lev motor nerves of one leg were recorded from an *in vitro* preparation of the thoracic nerve cord. Dep and Lev motor activity excited corresponding Dep and Lev muscles of a computational crayfish leg model (AnimatLab.com) to lower and raise the model leg, respectively. The resulting model leg movements controlled mechanical stimulation of the real CBCO stretch receptor of the *in vitro* preparation and excited CBCO afferent responses that completed the proprioceptive feedback loop in real time. The feedback loop was opened by uncoupling motor nerve responses to the corresponding model muscles. Exposure of the preparation to a muscarinic agonist (oxotremorine) induced an active state in which resistance reflexes to leg perturbation reversed to become assistance reflexes and irregular low-frequency (~1/30s) Lev/Dep motor burst pairs occurred when the feedback loop was open. Closing the feedback loop accelerated the motor rhythm three-fold, restructured motor bursts and increased the reproducibility of each burst. In closed loop, bursts began more abruptly, reached a high spiking frequency and ended earlier than bursts in open loop. Spike train analysis of motor nerve activity revealed that the firing patterns of most MNs differed significantly between closed and open loop conditions. When the loop was closed, three principal classes of MN activity are apparent: i) MNs active before the high frequency burst discharge , called pre-burst MNs, ii) MNs discharging only at the onset of bursts, called burst onset MNs and ii) MNs active during bursts, called in-burst MNs. In open loop, these patterns changed or disappeared during bursts. In each experiment (n=8), burst onset MNs are involved in assistance reflex and their initial firing rates in closed loop occurred earlier, increased more quickly to a higher level and ended also earlier than under open loop condition. The in-burst MNs often followed the burst onset MNs with a phasic discharge that occurred earlier and with a higher frequency than in open loop. These burst changes produced a more abrupt, faster, shorter and regular leg movement during each locomotion cycle when the feedback was closed.

Disclosures: **J. Bacque-Cazenave:** None. **B. Chung:** None. **D. Cattaert:** None. **W. Heitler:** None. **D.H. Edwards:** None.

Poster

607. Motoneuron Excitability: Afferent Input

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 607.14/O24

Topic: D.13. Motor Neurons and Muscle

Support: Davee Foundation grant

Title: Electrophysiological responses to joint rotation in acute stroke

Authors: ***N. L. SURESH**[1], J. EWOLDT[2], E. LAZZARO[1], G. JARAMILLO[1], W. Z. RYMER[1]; [1]Sensory Motor Perf Prgm, Rehabil. of Chicago, Chicago, IL; [2]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: The most common clinical test used to assess spasticity is the modified Ashworth test(MAS). Although weaknesses in the MAS test are largely acknowledged, it is still the standard measure used to characterize the level of resistance to stretch in spasticity. In stroke survivors, the MAS is used to identify the 'catch' angle as well a generalized resistance to joint rotation, the resultant score reflects both and therefore does not provide information that would allow a differentiation of one versus the other. The goal of our study was to conduct the MAS test and to assess differences between acute and chronic stroke survivors while tracking the results over a period of several months. Our objective was to quantify the differences in the nature of the stretch response, i.e., a sudden catch versus overall resistance, as well as to track any changes, particularly in our acute subjects, over time. Our methods involved conducting the MAS test with added sensors to quantify changes in joint angle position, joint angle velocity and EMG activity in the biceps muscle in response to rotation of the elbow joint. We tested two chronic and two acute stroke survivors over a period of 3 months. The subjects were comfortably seated in a chair with the arm initially at rest. Surface EMG electrodes were placed on the subjects' biceps and triceps to characterize muscle responses, if any. An electronic goniometer was placed across the elbow joint, and an accelerometer was placed on the lower arm. Data was digitized and recorded on a laptop computer. Our research physical therapist then positioned the joint in the maximum flexed position and slowly rotated the joint to the maximum extension over a period of 1 second for five trials, separated by 15 seconds each. These tests were also done with the arm rotated as fast as possible for five trials. The EMG onset time, as well as duration and magnitude of the EMG response were quantified. The catch angle and change in angular

velocity were derived from the goniometer and accelerometer data. Our results show that in the chronic stroke survivors there was a significant EMG response that lasted longer than the stretch duration, as well as a consistent 'catch'. The resistance to stretch occurred subsequent to the 'catch'. In our acute subjects, the predominant response involved a resistance to stretch, with few subjects exhibiting a catch angle, the EMG response was transient and increased in duration and amplitude over the three month testing period. These differences between acute and chronic stroke survivors could be attributed to changes in passive muscle properties that develop over time as well as change in motoneuron excitability that occur over time post-stroke.

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Poster

608. Cerebellum: Circuits and Function

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 608.01/O25

Topic: D.14. Cerebellum: Central Physiology

Title: Prefrontal cortex modulation of cerebellar motor learning

Authors: *M. T. DE JEU, P. J. HOLLAND, C. M. PARISIUS;
Erasmus MC, Rotterdam, Netherlands

Abstract: While the cerebellum undoubtedly plays a role in motor control and motor learning, there is increasing anatomic and electrophysiological evidence (Kelly and strick, 2003; Watson et al., 2009, 2014) for a functional connection between the Prefrontal Cortex (PFC) and the cerebellum that could affect these processes. However, the behavioral implications of this connection are still unknown. We posit that inputs from the Prefrontal Cortex (PFC) could modulate motor learning. In order to investigate this hypothesis, lesions were induced in the medial and ventral PFC of adult c57bl/6 mice and their consequences on motor behavior were studied. Motor performance and motor learning was assessed using the rotarod task and by using a cerebellar specific eye movement task. The lesioned animals were grouped according to their motor learning behavior in comparison to the average learning rate of control and sham operated animals. For each learning task, a histogram of the control data was made and the upper 20th and the lower 20th percentile was used to calculate the cutoff points that defined the high learning (HL), medium learning (ML) and low learning (LL) groups. The day 1 latency to fall was analyzed for possible effects of the lesions on the baseline motor performance in the rotarod task. No significant differences in the distribution of baseline motor performance between the groups

were found. The baseline eye movements (vestibulo-ocular reflex, optokinetic reflex and visual-enhanced vestibulo-ocular reflex) indicated also no performance impairment between these groups. Comparing the 3D reconstructed lesion sites of the different motor learning groups (i.e. HL, ML and LL) revealed that lesions in the lateral and ventral orbital regions of the prefrontal cortex reduces motor learning and the consolidation of the learned task, whereas lesions in the prelimbic and medial orbital regions of the prefrontal cortex has only very limited effects on these motor learning processes. These results demonstrate that lesions in specific PFC regions have a clear effect on motor skill acquisition, including cerebellar specific motor skill acquisition. These results imply that the PFC can modulate the cerebellum and thereby influence motor learning.

Disclosures: **M.T. De Jeu:** None. **P.J. Holland:** None. **C.M. Parisius:** None.

Poster

608. Cerebellum: Circuits and Function

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 608.02/O26

Topic: D.07. Vestibular System

Support: NSERC Discovery Grant LRB

Title: Depression of the cerebellar vermis alters the direction of postural sway to a vestibular perturbation

Authors: ***C. LAM**[1], C. TOKUNO[2], L. R. BENT[1];
[1]Human Hlth. and Nutritional Sci., Univ. of Guelph, Guelph, ON, Canada; [2]Kinesiology, Brock Univ., St. Catherines, ON, Canada

Abstract: Background: Balance is best maintained with the integration of available sensory input. The vestibular system reports on accelerations of the head and this information can be manipulated by a technique called stochastic vestibular stimulation (SVS). SVS involves passing an electrical current behind the ears, which alters the firing of vestibular afferents and generates a reflexive postural sway response. The sway occurs in the intra-aural direction so when facing forward the response is in the mediolateral (ML) direction and when the head is turned over the shoulder the response occurs anterioposteriorly (AP) [1]. This response also incorporates proprioceptive input from the neck and it is postulated that the cerebellum plays an important role in the generation of this appropriate postural response. **Aim**: To determine if cerebellar depression modulates the postural sway direction to a vestibular stimulus. **Methods**: Twenty

subjects (age 19-27) were tested in one of two groups, a test group, where subjects received continuous theta burst stimulation (cTBS – to cause cerebellar depression), and sham, where subjects received paired pulse TMS. SVS (±2 mA, 0-20 Hz) was delivered for six trials of 90 seconds with the head facing either forward or over the left shoulder. Subjects then received TMS over the cerebellar vermis using a MagStim rapid^2 stimulator (test: cTBS, 600 stim over 40 s at 100% AMT; or sham: 2 stim, 10 ms apart at 50% AMT) [2]. Following TMS, six more trials of SVS were repeated. Shear data were collected using an AMTI force plate and kinematic head position was collected using an Optotrak 3D Investigator. Cumulant density plots of the shear data to SVS were generated and shear axes were rotated 180^o to determine the direction of sway based on the angle of highest correlation. **Results**: There were no significant changes in head position for any condition. Head-referenced sway direction did not significantly differ with head forward for either test or sham conditions. With the head turned over the left shoulder there was no change in the sham condition but there was a significant change in sway to a more ML direction after cTBS (88.2^o to 95.2^o, p=0.017). **Discussion**: By depressing the function of the cerebellum we were able to evoke a change in the postural response to a vestibular perturbation from AP to a more ML sway. This could be due to the inability of the cerebellum to integrate neck and vestibular input to generate directionally appropriate postural responses. This work provides further insight into how our body processes various sensory input to help control our posture and balance. [1] Lund, Broberg (1983) Acta Physiol Scand; [2] Popa et al (2010) Brain Stim

Disclosures: **C. Lam:** None. **C. Tokuno:** None. **L.R. Bent:** None.

Poster

608. Cerebellum: Circuits and Function

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 608.03/O27

Topic: D.14. Cerebellum: Central Physiology

Title: Purkinje cell activity modulated by the transcranial direct current stimulation (tDCS) in rats

Authors: N. VUKMER[1], P. DOMENIG[1], K. SHIN[1], *H. LU[2];
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Abstract: Cerebellar ataxia encompasses a wide range of neurological disorders characterized by a lack of coordinated movements. Recently, transcranial direct current stimulation (tDCS) has

been shown to be a possible therapy of cerebellar ataxia in humans. Animal studies have demonstrated that the cerebellar tDCS is capable of modifying the output of the motor cortex through the cerebello-thalamo-cortical pathway. However, the cellular mechanism of the Purkinje cells due to the cerebellar tDCS treatment is unclear. In this study, extracellular potentials were recorded from Purkinje cells in Sprague Dawley rats to determine if the cerebellar tDCS altered the activity of these cells. The tDCS was delivered using a metal electrode positioned immediately posterior to the recording site in crus I or II (anode, intensity: 100 - 200 μA) for 20 min. The recordings from four Purkinje cells showed an average increase in firing rate of 26.8% during the application of the cerebellar tDCS. Only one cell with a fluctuating base firing rate showed a decrease in the average firing rate during the stimulation. From the same recordings, local field potentials were analyzed using power spectrum in which no significant change was observed to the main peak at 2 Hz. In one case (tDCS with 200 μA), the amplitude of the second peak between 7 and 8 Hz increased. The results support the previous studies that electrophysiological changes occur in the motor cortex as a consequence of altered Purkinje cell firing. In order to investigate the mechanism of these changes, future experiments will be performed with simultaneous recordings from Purkinje cells and motor cortical neurons with the application of tDCS.

Disclosures: **N. Vukmer:** None. **P. Domenig:** None. **K. Shin:** None. **H. Lu:** None.

Poster

608. Cerebellum: Circuits and Function

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 608.04/O28

Topic: D.14. Cerebellum: Central Physiology

Support: NIH/NCATS KL2 TR000102

NIH NRSA F30DC014198

Title: Cerebellar tDCS alters resting-state connectivity in cerebro-cerebellar cognitive networks

Authors: ***A. M. D'MELLO**[1], D. SHOOK[1], W. HAYWARD[2], P. E. TURKELTAUB[2,3], C. J. STOODLEY[1];
[1]American Univ., Washington, DC; [2]Georgetown Univ. Med. Ctr., Washington, DC; [3]MedStar Natl. Rehabil. Hosp., Washington, DC

Abstract: The posterolateral cerebellum is functionally connected to cortical networks implicated in cognition, including the default mode (DMN) and fronto-parietal cognitive control and attention networks. In addition, during language tasks the right posterolateral cerebellum is functionally activated in conjunction with supratentorial language regions, such as the inferior frontal gyrus. Disrupted functional connectivity between the right posterolateral cerebellum and supratentorial language regions has been noted in neurodevelopmental disorders such as autism, and might underlie language deficits in these populations. However, the role of the cerebellum in modulating long-distance cortical regions has not been directly explored. Our aim was to examine the effects of cerebellar transcranial direct current stimulation (tDCS) on functional connectivity between the cerebellum and cerebral cortical regions. We hypothesized that right cerebellar tDCS would alter functional connectivity between the right posterolateral cerebellum and cerebral regions involved in language and cognition. We applied 20min of 1.5 mA anodal tDCS over the right posterolateral cerebellum (1 cm down and 4 cm lateral from the inion) in healthy young adults (n=8; μ=26.5 years). Eight minutes of resting-state data were acquired pre- and post-tDCS. Functional connectivity between cerebellar right Crus I and the pars opercularis of the left inferior frontal gyrus decreased post-tDCS ($p < 0.05$, FDR corrected). These results are consistent with the functional and anatomical connections between the right posterolateral cerebellum and contralateral supratentorial language regions. The current results suggest that cerebellar tDCS is able to modulate cerebro-cerebellar circuits involved in language and cognition.

Disclosures: **A.M. D'Mello:** None. **D. Shook:** None. **W. Hayward:** None. **P.E. Turkeltaub:** None. **C.J. Stoodley:** None.

Poster

608. Cerebellum: Circuits and Function

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 608.05/O29

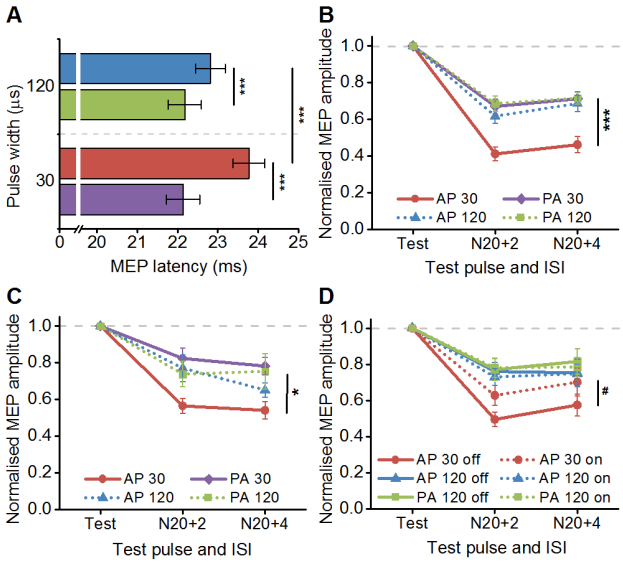
Topic: D.14. Cerebellum: Central Physiology

Support: MRC Grant 6EKW

Title: Differential modulation of interneuron circuits in human motor cortex by afferent input and cerebellar direct current stimulation

Authors: ***R. HANNAH**, D. AUSTIN, J. C. ROTHWELL;
UCL Inst. of Neurol., London, United Kingdom

Abstract: We tested the hypothesis that distinct excitatory circuits in primary motor cortex (M1) are differentially affected by sensory input from the hand (Ni et al. 2011, J Neurophysiol) and by transcranial direct current stimulation over the cerebellum (cDCS). A controllable pulse parameter TMS (cTMS; Rogue Resolutions Ltd.) device was used to activate distinct independent interneuron circuits in the hand area of M1 by changing the coil orientation (posterior-anterior, PA; anterior-posterior, AP) and TMS pulse width (30 and 120 μs). An electrical stimulus to median nerve or digital nerves provided sensory input. We measured its effect on the amplitude of MEPs elicited by the different directions/widths of pulses ~25ms later (inter-stimulus intervals: N20 latency +2 and +4 ms; short latency afferent inhibition, SAI). Anodal or sham cDCS (2 mA) was applied concurrently in different sessions to examine any cerebellar influence on SAI. Experiments were performed whilst participants maintained voluntary muscle contraction (5-10% MVC). Single motor unit potentials (Exp. 1, n=6) and surface EMG (Exp. 2, n=20; Fig A) recorded from the first dorsal interosseous confirmed that short AP pulses (AP30) recruited longer latency inputs than long AP and short/long PA pulses. SAI tested with median nerve stimulation was greater for AP30 responses compared with the other three conditions (Exp. 2, n=20; Fig B). Similar effects were found with digit stimulation (Exp. 3, n=10; Fig C), implying that the differential response to AP30 was not due to a preference for cutaneous versus muscle afferent input. Online anodal cDCS reduced SAI for the AP30 condition only (Exp. 4, n=11; Fig D). Short AP-oriented pulses appear to activate interneuron populations distinct from those activated by long AP- and short/long PA-oriented pulses. The AP30-sensitive populations are associated with the longest latency MEPs, and appear more sensitive to SAI. cDCS reduced the inhibition associated with AP30-sensitive interneurons implying that these populations receive indirect sensory inputs from the cerebellum.



Influence of pulse width and coil orientation on MEP latencies (**A**) and SAI tested with median nerve (**B**) and digit stimulation (**C**). Interaction of anodal cDCS with SAI (nerve) tested with different pulse widths and coil orientations (**D**). Off refers to measurements prior to cDCS and On refers to measurements during. ***P < 0.001 for comparisons between conditions (**A**), ***P < 0.001 between AP30 and other conditions (**B**), *P < 0.05 between AP30 vs. AP120 and PA30 (**C**), $^{\#}P$ < 0.05 for comparisons between AP30 Off vs. On cDCS (**D**).

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Poster

608. Cerebellum: Circuits and Function

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 608.06/O30

Topic: D.14. Cerebellum: Central Physiology

Support: Italian Ministry of Healthcare RF-2011-Q2348213

Italian Ministry of Healthcare RF-2010–2319611

Title: Effects of transcranial direct current stimulation of the cerebellum on brain resting state oscillatory and network activity

Authors: D. MATTIA[1], M. PETTI[1,5], L. ASTOLFI[1,5], M. MASCIULLO[2], I. PISOTTA[3], S. CLAUSI[6,4], M. LEGGIO[6,7], F. CINCOTTI[5], *M. MOLINARI[8];
[1]Neuroelectrical Imaging and BCI Lab. (NEILab), [2]SPInal cord REsearch Lab. (SPIRE),, [3]Lab. of Robotic Rehabil. (NeuroRobot Lab., [4]Ataxia Lab., Santa Lucia Foundation, IRCCS, Rome, Italy; [5]Dept. of Computer, Control and Mgmt. Engineering,, Sapienza Univ. of Rome, Rome, Italy;, Rome, Italy; [6]Psychology, Fac. of Med. and Psychology Sapienza Univ. of Rome, Rome, Italy; [7]Ataxia Lab, Santa Lucia Foundation, IRCCS, Rome, Italy, Santa Lucia Foundation, IRCCS, Rome, Italy, Rome, Italy; [8]Santa Lucia Fndn., Roma 00179, Italy

Abstract: Transcranial direct current stimulation (tDCS) of the cerebellum can offer new insights on the cerebellar function and disorders by modulating non invasively the activity of cerebellar networks. Taking into account the functional interplay between the cerebellum and the cerebral cortex, we addressed the effects of the unilateral cerebellar tDCS on the electroencephalographic (EEG) oscillatory activity and the cortical network organization at resting state. Eight healthy volunteers participated in the study (age: 30.1±5.4 years). Three randomized stimulation sessions, anodal, cathodal tDCS (20 min duration; 2 mA; active electrode positioned over the right cerebellar hemisphere) and sham were performed. Scalp EEG potentials (48 position electrode cap) were recorded (commercial EEG system) during 2 minutes of eyes-closed resting state, before (pre) and after (post- 15, 35 and 60 min) each session. After data preprocessing, the power spectral densities (PSD) were computed and averaged within 4 frequency bands (from theta to gamma band). Single subject PSD values obtained after anodal and cathodal tDCS were contrasted against sham PSD (t-test; $p<0.5$, post-hoc correction). Effective connectivity was estimated by means of Partial Directed Coherence (PDC) and synthetic indices describing the network topology were extracted based a graph theoretical approach (global efficiency, local efficiency). Analysis of variance (ANOVA; within factor "latency"; 4 levels: pre, post-15, post-35, post-60) was carried out for each index, stimulation type and frequency band. At post-15 min from anodal stimulation, a significant increase (synchronization) in the alpha and beta PSDs was observed mainly over the left centro-parietal and posterior temporal scalp regions. At post-15 min, cathodal tDCS resulted in a significant theta band synchronization occurring over the central and parietal midline and the bilateral centro-parietal regions. Such synchronization lasted no longer than 15 min. Only a significant increment of local efficiency was observed after 15 min from the anodal tDCS. Present data demonstrate different modulatory effects of unilateral cerebellar anodal/cathodal tDCS on brain oscillatory rhythms. Lateralized sensorimotor rhythm synchronization would be in line with current interpretation of a reduced cortical motor excitability after anodal cerebellar tDCS. Under this condition, the topology of brain networks seems to shift towards a higher segregation of information flow. Cerebellar modulation on diffuse midline thalamo-cortical circuits might account for the observed effects of cathodal tDCS.

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Poster

608. Cerebellum: Circuits and Function

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Program#/Poster#: 608.07/O31

Topic: D.14. Cerebellum: Central Physiology

Support: The Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), 5 U24 AA014811-07, subaward 53253G P1660 7808 211

Title: Cerebellar activity during a visually cued finger tapping task in adolescents with Fetal Alcohol Spectrum Disorder (FASD): a Magnetoencephalographic (MEG) study

Authors: *C. M. GARCIA[1], P. W. KODITUWAKKU[2], C. D. TESCHE[2];
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Abstract: Exposure to substantial amounts of alcohol *in utero* is known to produce structural and functional brain anomalies in offspring. While ethanol-induced abnormalities are found throughout the brain, some regions (e.g. cerebellum, caudate) appear to be more affected than other regions. Converging evidence from animal models and human imaging studies has shown that prenatal alcohol exposure is associated a range of alterations in the cerebellum, including a reduction in volume, changes in the surface area and a thinner vermis. Therefore, it is reasonable to hypothesize that the functions that are held to be mediated by the cerebellum -balance, bimanual coordination, attention (Norman et al., 2009; Luo, 2012)-are impaired in children with prenatal alcohol exposure. It can also be expected that alcohol-exposed children are impaired at internal timing of both motor and non-motor tasks, since the cerebellum plays a key role in timing (Tesche and Karhu, 2000; Spencer et al., 2003). In the current research, we probed differences in brain dynamics in children with fetal alcohol spectrum disorders (FASD) and aged-matched controls during performance of a visual-motor task, which is known to involve the cerebellum. The FASD group comprised 20 children who had been diagnosed having a prenatal alcohol diagnosis (FAS, partial FAS, and ARND); the control group included 22, age-matched (12-19 years of age) children who did not have prenatal exposure to alcohol. Data were recorded with a 306-channel MEG array. The finger tapping task employed 6 - 8 visually presented cues. Subjects were told to make a motor response with the right index finger to presented visual stimuli. The visual stimuli were presented for 350 ms, and had an interstimulus interval of 750 ms. BrainStorm (Tadel et al. 2011) was used to extract spatio-temporal patterns of activation in the Rt Crus I and Vermis time-locked to the initial four motor responses. The FASD group had less activation compared to the controls. In the Rt Crus I, amplitude differences were found prior to the motor response to the 1st cue and 4th cue, but not the 2nd and 3rd cues. In the Vermis,

amplitude differences were present prior to the motor response to the first cue. Little or no differences were present prior to motor responses to the 2nd and 3rd cues. For the 4th cue, amplitude differences are only present after the motor response. Behavioral reaction times were also significantly different with the FASD group having both longer reaction times and greater temporal variability. The differences in behavioral reaction times and cerebellar activation by the FASD group suggests a disruption of the cerebellum in producing and maintaining timed movements.

Disclosures: C.M. Garcia: None. **P.W. Kodituwakku:** None. **C.D. Tesche:** None.

Poster

608. Cerebellum: Circuits and Function

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 608.08/O32

Topic: D.14. Cerebellum: Central Physiology

Support: BMBF Grant 01 EO 1401

Title: Updating inverse models for head movement control does not require cerebellar integrity

Authors: N. LEHNEN[1], *S. GLASAUER[2], M. SAğLAM[3];
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Abstract: The cerebellum is considered essential for implementing internal models, of which inverse models generate motor commands for a desired movement and forward models predict sensory consequences of applied motor commands. Cerebellar damage impairs internal model adaptation, leading to deficient motor performance against perturbations or changes in plant properties. However, in recent reaching studies, cerebellar patients could adapt to gradually applied perturbations. This was linked to their remaining ability to learn inverse model dynamics. Recently, we showed that cerebellar ataxia patients could also re-optimize head movement kinematics during large gaze shifts when head dynamics were perturbed by an experimental increase in head inertia. Here, we investigate whether this optimization depends on updating the intended movement, inverse or forward models, or all of them. Using a control systems model, we assessed the contributions of inverse and forward model plasticity on updating head movement kinematics to an increase in head inertia in nine cerebellar ataxia patients and ten healthy controls. We found that the experimentally observed changes in head movements of cerebellar patients are best explained by assuming that the inverse model, but not

the forward model, is adapted to match the new plant characteristics. We show that by adapting the inverse model it is still possible to optimize head movement kinematics, i.e., to decrease suboptimal oscillations, maintain optimal movement durations, and increase peak velocity towards the new optimum. This suggests that the residual extra-cerebellar motor control network can implement inverse models, update intended movements and re-optimize without correctly predicting sensory consequences of action.

Disclosures: **N. Lehnen:** None. **S. Glasauer:** None. **M. Sağlam:** None.

Poster

608. Cerebellum: Circuits and Function

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 608.09/O33

Topic: F.02. Animal Cognition and Behavior

Title: Differential roles of the cerebellar hemisphere and dentate nucleus in temporal processing across sub- and supra-second durations

Authors: *E. PETTER, N. A. LUSK, W. H. MECK;
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Abstract: Elijah A. Petter, Nicholas A. Lusk, and Warren H. Meck, Department of Psychology and Neuroscience, Duke University, Durham, North Carolina, USA The ability to accurately and precisely time intervals from ten's of milliseconds to hours relies on coordinated activity across multiple brain regions. Two of the most investigated regions are the cerebellum and striatum. Based on evidence from both lesion and neurodegenerative studies, the canonical belief is that the cerebellum mediates timing in the sub-second range (i.e., durations than 1s). A major confound in many of these earlier studies was the performance of a timing task exclusively in either the sub- or supra-second range. Compounded by the fact that many studies differ in task demands (e.g., comparison, production, reproduction, and discrimination), it is unclear how to interpret these results. The neural architecture of the cerebellum makes it an ideal structure for temporal processing, with Purkinje cells (PCs) within the cerebellar hemispheres integrating temporal aspects of salient stimuli. Previous work has shown that tonic firing rates of PCs can be modulated to reflect a criterion duration. Furthermore, neural activity in downstream cerebellar deep nuclei are modulated by the temporal regularity of stimulus presentations. In the current study, we attempted to identify the role of the cerebellum in both sub- and supra-second timing using the duration bisection task with anchor durations of 200 vs. 800 ms and 2 vs. 8 s alternating within subjects and between sessions. In order to investigate the different components

of the cerebellar-striatal network, our study included groups with bilateral excitotoxic lesions to either the dentate nucleus (the primary cerebellar output to the striatum) or the lateral cerebellar hemisphere (containing PC projections to the dentate nucleus) of sprauge dawley rats. Preliminary findings suggest differences in temporal accuracy and precision, evidenced by shifts in the point of subective equality and increased variability among experimental and sham-lesioned groups. Specifically there was a severe disruption in sub-second timing for hemisphere lesioned rats, and a rightward shift in point of subjective equality in supra-second durations for dentate lesioned rats.This study is the first to examine the different roles of the cerebellar hemisphere and dentate nucleus in time perception across sub- and supra-second durations. Taken together, the evidence suggests a dissociation in the roles of the cerebellar hemisphere and dentate nucleus in terms of temporal *Initiation, Continuation, and Adjustment.*

Disclosures: E. Petter: None. **N.A. Lusk:** None. **W.H. Meck:** None.

Poster

608. Cerebellum: Circuits and Function

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 608.10/O34

Topic: F.02. Animal Cognition and Behavior

Title: Early postnatal methylazoxymethanol administration leads to cerebellar hypoplasia and supra-second timing deficits in adult rats

Authors: *N. A. LUSK, E. A. PETTER, W. H. MECK;
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Abstract: Methylazoxymethanol (MAM), a powerful antimitotic, has been extensively used to affect rodent CNS development. When MAM is administered at critical developmental periods neuroanatomical effects in adulthood have been particularly apparent in the cerebellum with reductions in size as well as disruption of the cytoarchitecture. Specifically, purkinje cells retain immature characteristics as well as contain multiple climbing fiber innervations. Functional changes have also been observed as evidenced by impairments in reversal learning, set shifting, reaction time, and interval timing depending upon the age of treatment. Here we show that MAM injected during postnatal days 1-4 produced an 18% reduction in cerebellar weight at 150 days of age, with relatively little change in the weight of other regions such as the forebrain or striatum (3% and 6% reductions, respectively). As the cerebellum has been shown to be involved in temporal processing in the msec-sec range, we investigated the effects of MAM induced cerebellar hypoplasia on timing using a temporal bisection procedure with 2-sec vs. 8-sec anchor

durations. To evaluate differences in temporal processing we used the point of subjective equality (PSE), the duration between the two anchor durations that is classified as subjectively 'long' 50% of the time, and the Weber fraction (WF), which provides a measure of temporal sensitivity accounting for the just noticeable difference between durations normalized to the PSE. Our findings reveal that reductions in cerebellar weight correlate with a decrease in temporal sensitivity as measured by the Weber fraction (WF), $R2 = 0.51$, $p < 0.002$. Moreover, there was a significant between-group effect on the WF, $F(1,13) = 9.9$, $p < 0.0001$, and the PSE, $F(1,13) = 6.36$, $p < 0.05$, indicating a decrease in temporal sensitivity and an underestimation of signal duration for the MAM group. Taken together, the current study identifies the potential importance of the cerebellum for timing in the supra-seconds range. Although the effects of MAM were predominantly observed in terms of cerebellar volume, more subtle changes to cytoarchitecture in other brain areas as well as inter-region connectivity cannot be ruled out. As timing and time perception are believed to rely on multiple brain areas as well as distinct regions within the cerebellum, further work needs to be done in order to determine how selective lesions of the cerebellar hemisphere and dentate nucleus affect timing for both sub- and supra-second durations (see Petter, Lusk, & Meck, 2015 - SfN Abstract).

Disclosures: **N.A. Lusk:** None. **E.A. Petter:** None. **W.H. Meck:** None.

Poster

608. Cerebellum: Circuits and Function

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 608.11/O35

Topic: D.14. Cerebellum: Central Physiology

Support: CONACyT: 326816

CONACyT: 294146

CONACyT: 575913

Title: Fos expression in Purkinje cells by olfactory stimulation in male rats

Authors: ***Z. S. HERNÁNDEZ**[1], A. TAMARIZ[1], L. VÁSQUEZ[1], G. ARANDA-ABREU[2], R. TOLEDO[2], G. CORIA-AVILA[2], J. MANZO[2], L. I. GARCÍA[2];
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Abstract: There have been attributed to the cerebellum multiple and varied roles of such importance as the coordination of intentional and spontaneous movements, regulation of posture and vestibular function, participation in the specificity of reflex responses, as well as its participation in memory and emotional experience, sex and orgasm, language, planning and forecasting; and the ability of perception. Studies have shown that stimulation distance in male rats by sexual cues (stimulation without contact), and the acquisition of experience in sexual behavior significantly increases the expression of Fos in the granular layer in each lobe of the cerebellum. Although this activity could corresponds to sensory stimulation (visual, auditory or olfactory) or the motor execution. There is almost no information on the cerebellum in sensory integration, particularly about smelling. The objective of this study is to analyze and compare the expression of Fos protein in the cerebellar vermis in Purkinje layer of male rats who have performed sexual behavior after being olfactory stimulated. Wistar male rats (250-300 g) experienced copulatory sessions when they were placed for 24 hours inside a transparent acrylic cubic box (30 X 30 X 60 cm) with a double bottom. They remained within 70 min, 10 min initial habituation, pre olfactory stimulation; which consisted on placing between the double bottom of the chamber, a vessel containing the controls, almond and a receptive female stimulus. The test lasted 60 minutes, passing a rat and a stimulus at a time. At the end of the test, rats were anesthetized with an overdose of pentobarbital sodium (60 mg / kg), and a transcardiac perfusion was performed. The cerebellar vermis was processed and underwent immunohistochemical reaction to detect the Fos protein. The expression of Fos in Purkinje neurons in the cerebellar vermis of male rats is diminished. That pattern in all three groups decreased with the acquisition of experience in sexual behavior. According to the obtained results from the analysis of Fos in the layer of Purkinje we observed that these were completely contrary to those obtained from the analysis in the granular layer of the cerebellar vermis (increased expression of the protein). To find the relationship of this finding we discussed complies with the principle described as long-term depression, essential for memory consolidation and learning process.

Disclosures: Z.S. Hernández: None. **A. Tamariz:** None. **L. Vásquez:** None. **G. Aranda-Abreu:** None. **R. Toledo:** None. **G. Coria-Avila:** None. **J. Manzo:** None. **L.I. García:** None.

Poster

609. Bimanual and Interlimb Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 609.01/O36

Topic: D.17. Voluntary Movements

Support: National Science Foundation BCS-1153034 “Collaborative Research: Sensory Integration and Sensorimotor Transformations for Dexterous Manipulation”

Title: Assessing control mechanisms and leader-follower roles in human-human and bimanual interactions during object manipulation

Authors: *K. MOJTAHEDI, M. SANTELLO;
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Abstract: Physical interactions can be intrapersonal, e.g., manipulating an object using two hands, or interpersonal, e.g., transporting an object with another person. In both cases, each agent is required to ensure spatial and temporal relations among the effectors to attain a specific performance goal, i.e., preventing the object from slipping or tilting. However, little is known about how humans coordinate their physical interactions for object manipulation, and in particular how the role of each participant emerges during collaborative tasks. We investigated joint action using an object-balancing task performed by two agents or bimanually by the same agent. The task goal was to grasp and move a U-shape grip device while keeping it horizontal by observing a bubble level located on the object. We asked participants to move the grip device at two predefined heights. The task consisted of static (holding) and dynamic (moving) phases. Auditory cues were given to specify the initiation of the dynamic phases. We measured forces and moments exerted on each handle and grip device kinematics. Three groups of subjects, bimanual (Bi, 9 subjects), human-human (H-H, 9 dyads), and Leader-Follower (L-F, 9 dyads), participated in the experiment. L-F group is similar to H-H group, with the exception that only the leader was given the auditory cues. We quantified (1) the role of potential asymmetries for interlimb coordination during bimanual interaction (Bi group), (2) how the role of each agent emerges during physical interactions (H-H group), and (3) behavioral features to identify the leader versus follower roles (L-F group). Continuous wavelet transform (Mojtahedi et al., 2015) revealed that dyads relied more on feedback control than individual subjects performing the task bimanually. Furthermore, the results of cross wavelet spectrum analysis showed that the extent to which the rate of moments was synchronized was higher in dyads than individual subjects. Therefore, both of these performance metrics indicate that dyads were significantly more accurate than individual subjects. Furthermore, all subject groups were characterized by a ‘leader-follower’ relation. Specifically, in the Bi group, the dominant arm was identified as leading the physical interactions in all movement phases. Interestingly, dyads in H-H group exhibited the same role specialization as the L-F group, even though leader-follower roles were not explicitly specified for the H-H group. These preliminary results point to an asymmetrical role assignment during physical interactions involving two limbs of the same or different agents. The underlying sensorimotor mechanisms remain to be investigated.

Disclosures: K. Mojtahedi: None. **M. Santello:** None.

Poster

609. Bimanual and Interlimb Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 609.02/O37

Topic: D.17. Voluntary Movements

Title: Somatosensory electrical stimulation added to motor practice modifies neuronal excitability but does not have additive effects on interlimb transfer in humans

Authors: *M. P. VELDMAN[1], I. ZIJDEWIND[2], N. A. MAFFIULETTI[3], T. HORTOBÁGYI[1]; [1]Ctr. for Human Movement Sci., [2]Dept. of Neurosci., Univ. Med. Ctr. Groningen, Groningen, Netherlands; [3]Neuromuscular Res. Loboratory, Schulthess Clin., Zurich, Switzerland

Abstract: Introduction: Sensory input modifies motor function. Previous data showed that sensory input in the form of somatosensory electrical stimulation (SES) can increase stroke patients' manual motor function. An understanding of how such modifications occur is important in the rehabilitation of patients with sensory deficits. In addition, SES bilaterally activates sensory cortices that are directly connected to the primary motor cortex. These findings led to the hypothesis that SES combined with motor practice (MP) could increase interlimb transfer of a motor skill. We examined if SES added to motor practice (MP) could augment interlimb transfer of a visuomotor skill and if changes in neuronal excitability mediated this transfer effect. Methods: Young adults (18-30y, n = 25) received either MP, SES, or MP+SES. Interlimb transfer was quantified by the reduction in deviation in degree from the preprogrammed template measured in the left-transfer hand after a right-hand intervention. MP consisted of 300 5-s-long visuomotor trials with the right hand. SES consisted of 1-s-trains of weak electrical stimulation of the radial and median nerves above the elbow at 10 Hz. Single- and double pulse transcranial magnetic stimulation (TMS) was used before and after the visuomotor intervention to determine changes in neuronal excitability. Results: The magnitude of transfer of the visuomotor skill was significant after the three interventions combined ($p < 0.001$) and separately (MP: 4.4°; 12%, SES: 3.0°; 6%, MP+SES: 3.2°; 8%). However, the magnitude of interlimb transfer was not different between groups (Group by Time interaction, $p = 0.35$). Corticospinal excitability in the non-practice and non-stimulated left hand increased more after SES (54%) compared to MP (1%) and MP+SES (-14%) ($p = 0.023$), possibly mediated by a 8% decrease in interhemispheric inhibition after SES ($p < 0.05$). However, there were no correlations between interlimb transfer and changes in TMS metrics (all $p > 0.05$). Conclusion: MP and SES each can produce interlimb transfer but when combined, the individual effects are not additive and are likely mediated by different mechanisms. The observed crossed effects illustrated by the transfer of skill after SES can possibly accelerate the rehabilitation of patients with sensory deficits through mechanisms of motor cortical plasticity.

Disclosures: **M.P. Veldman:** None. **I. Zijdewind:** None. **N.A. Maffiuletti:** None. **T. Hortobágyi:** None.

Poster

609. Bimanual and Interlimb Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 609.03/O38

Topic: D.17. Voluntary Movements

Support: R01NS076589

R01NS090622

Title: Facilitation of triceps brachii motoneurons by contralateral elbow flexion

Authors: *I. ZIJDEWIND[1], M. A. PEREZ[2,3];
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Abstract: During strong unilateral contractions activity is not confined to the target muscles but contralateral homologous muscles also become active. During bilateral contractions however, transcranial magnetic stimulation (TMS) showed facilitatory connections between contralateral antagonistic muscles. Here, we examined the effects of unilateral contractions on contralateral activity, corticospinal (MEPs) and spinal excitability (CMEPs) in contralateral homologous and heterologous muscles. Eleven volunteers (5 females) were included in the study. Subjects performed maximal voluntary contractions (MVC) with either elbow flexors or extensors of the dominant side. During the contractions EMG, force and TMS evoked responses were recorded in the non-dominant muscles. In six subjects (3 females) additional experiments were performed to assess spinal excitability with transmastoid stimulation during maximal elbow flexion with the dominant arm and low force elbow flexion and extension with the non-dominant arm. MEP and CMEP were expressed as % of maximal M-wave (Mmax). During maximal elbow flexion significantly different amounts of contralateral associated EMG were observed in the biceps brachii (3.4% MVC, 2.3 SD) vs triceps brachii (10.6% MVC, 6.7 SD; p=0.007); whereas during maximal elbow extension, similar amounts of associated EMG were observed (biceps: 2.8% MVC, 2.6 SD; triceps: 3.2% MVC, 2.9 SD; p=0.67). Thus, activity in the triceps was greater during contralateral elbow flexion than extension (p=0.001). The MEPs data revealed similar results: a difference was observed in the triceps MEPs during contralateral flexion (34.4%

Mmax) vs extension (10.6% Mmax; P=0.03); whereas in the biceps no difference was found (flexion: 17.1% Mmax; extension 20.0% Mmax). The MEP data reflected mainly differences in associated activity because if we only selected MEPs with matched background EMG no difference in triceps MEPs were found (flexion: 8.6% Mmax; extension: 8.5% Mmax). In the triceps, CMEPs during contralateral elbow flexion were greater (15.4% Mmax, 8.1 SD) than CMEPs evoked during voluntary activation (at similar background EMG, 9.6% Mmax, 5.7 SD). During contralateral elbow flexion the excitability of the triceps increased significantly more than during extension. The data indicate that excitability changes were mainly situated on a spinal level. The results suggest that combining voluntary triceps activity with contralateral flexion could help to activate triceps motoneurons in subjects suffering from impaired voluntary drive.

Disclosures: I. Zijdewind: None. **M.A. Perez:** None.

Poster

609. Bimanual and Interlimb Control

Location: Hall A

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Topic: D.17. Voluntary Movements

Support: W911QY-12- C-0078 ProjectDoD,USA"Consequences of Loading on Postural- Focal Dynamics."

Title: Motor control efficiency in bimanual and collaborative tasks

Authors: E. J. AVILA MIRELES, *V. SQUERI, D. DE SANTIS, P. MORASSO, J. ZENZERI;
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Abstract: Many human-performed tasks are inherently unstable. These tasks are difficult to carry out because they are sensitive to different initial conditions and factors as neuromotor noise and external perturbations that can cause an unpredictable and unsuccessful performance. These peculiarities make them particularly suitable for investigating kinematic strategies used by humans to solve problems of stabilization. In previous studies, it was shown that trained subjects could stabilize a compliant tool in an unstable environment using two different control strategies: stiffness and positional. The first strategy is faster from the dynamics point of view, but more energy consuming. The second one is more efficient in terms of effort. When the participants were asked to perform the same task in a dyad, the results highlighted a beneficial effect of

collaboration in terms of effort. However, previous results focused only on the kinematic aspects of the task, without considering the muscular activity. The mechanisms that simultaneously accommodate kinematics and muscular aspects to achieve stability remain still unclear. To look into this interrelation, we asked 3 subjects, trained in the bimanual task, to grasp the handle of a bimanual robotic manipulandum, and to stabilize a virtual mass immersed in a saddle-like force field that provides instability, first bimanually and then forming dyads. During the task we acquired the kinematic data together with the corresponding EMG signals from 13 muscles of each arm. We computed the root mean square (RMS) of the EMG signals and an Effort Index evaluated from the kinematic data. To understand how a subject solves the stabilization problem, we first considered the bimanual condition. Both the evaluated indexes were greater for the stiffness strategy than for the positional one, underlining that the stiffness strategy is more costly in terms of effort. When subjects were solving the task as dyads, we found that the Effort Index was smaller for the positional strategy, as in the case of the bimanual condition. Conversely, the muscular activity provided no clear evidence that the muscular effort was systematically lower in the positional strategy. Indeed, the RMS values of the dyads in the positional strategy showed a non-uniform behavior and were very similar to or in some cases, even higher than in the stiffness condition. These results suggest that even if kinematic strategies can be easily generalized to different environmental conditions, such as dyadic collaboration, they may not be reflected by the strategies at a muscular level. These latter may be more sensitive to other factors, like predictability of the interaction.

Disclosures: **E.J. Avila Mireles:** None. **V. Squeri:** None. **D. De Santis:** None. **P. Morasso:** None. **J. Zenzeri:** None.

Poster

609. Bimanual and Interlimb Control

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Program#/Poster#: 609.05/O40

Topic: D.17. Voluntary Movements

Support: Institute of Advanced Active Aging Research

Grant-in-Aid for JSPS Fellow

Title: Modulation of corticospinal excitability of wrist muscles depending on the phase of cyclic illusory movement of the contralateral limb

Authors: *K. NAKAGAWA[1,2,3], Y. UMESAWA[4], Q. WEIHUANG[3], K. NAKAZAWA[1], M. G. FUJIE[5], H. FUJIMOTO[4], K. KANOSUE[3];
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Abstract: Symmetrical bimanual movements are more easily performed than asymmetrical movements (Swinnen, Nat Rev Neurosci, 2002). As a one of neural basis of the symmetrical tendency, corticospinal excitability of the resting wrist muscles modulates depending on the phase of cyclic voluntary movement of contralateral hand (Carson et al. J Physiol. 2004). The detailed neural mechanisms of the phase-dependent neural modulation in remote limb are still hardly known. In order to investigate the effect of kinesthetic sensation on the neural modulation, we tested whether just kinesthetic illusion (Goodwin et al. Science, 1972) as well as voluntary movement modulates corticospinal excitability depending on the phase of illusory movement. The experimental tasks were 1) voluntary movement, 2) kinesthetic illusion induced by tendon vibration (80Hz), 3) passive movement. Each task was periodical movement of left hand (0.75Hz). Transcranial magnetic stimulations of the left motor cortex were delivered during the phase of extension or flexion of left wrist, and then motor evoked potentials (MEPs) were recorded from of resting right forearm muscle (extensor and flexor). In each task, MEPs were divided into two movement phases (extension and flexion), and the significant differences in MEP amplitude between them were ascribed to the occurrence of the phase-dependent modulation. The results showed that kinesthetic illusion of the left wrist modulated the MEPs amplitude in the resting right wrist muscles depending on illusory movement phase just as observed during voluntary or passive movement. These results indicate that irradiation of motor commands during motor execution should not be a necessary condition for production of functional connection between bimanual hands. In conclusion, kinesthetic illusion of single limb may produce the phase-dependent modulation of corticospinal excitability of contralateral limb, which suggests the importance of kinesthetic sensation for the functional connection between bimanual hands.

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Poster

609. Bimanual and Interlimb Control

Location: Hall A

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Program#/Poster#: 609.06/O41

Topic: D.17. Voluntary Movements

Support: KAP-1.1-14/25 (Pazmany Peter cath. Univ.)

Title: Variances of joint configuration and muscle activity patterns during arm cycling against external resistances

Authors: M. MRAVCSIK[1], L. BOTZHEIM[2], N. ZENTAI[1], *J. LACZKO[1,2,3];
[1]Univ. of Pecs, Pecs, Hungary; [2]Fac. of Information Technol. and Bionics, Pazmany Peter Catholic Univ., Budapest, Hungary; [3]Wigner Res. Ctr. for Physics, Budapest, Hungary

Abstract: Variances of limb movement patterns depend on environmental forces. Here a motor task for human forelimbs is investigated in which the variance of the endpoint trajectory (hand path) assumed to be very small. 17 right-handed, able-bodied participants (Age: 23.76, ±2.33 y.) performed arm cycling movements under 3 resistance conditions (RC): low, moderate, high crank resistance on a MEYRA (Kalletal, Germany) ergometer. Surface EMGs were recorded from biceps, triceps, delta anterior, delta posterior. Positions of markers placed on the participant's arm were recorded by a ZEBRIS (Isny Germany) movement analyzer. Intersegmental angles in the shoulder, elbow and wrist were computed from marker positions. Time courses of joint angles and muscle activities (EMG amplitude) were segmented based on the number of cycles the subjects completed. The frames in which the elbow reached the most flexed positions were used to define the starts of separate cycles. Joint angle and EMG data obtained in separate cycles were time normalized and their variances across cycles in each condition for each participant were computed. The variances obtained in low, medium and high resistances were compared applying repeated measures ANOVA. When cycling with 2 arms, it was found that for the left arm there is a significant difference in the muscle activity variances obtained in low and high RCs. For the right arm, significant differences were found between low and high and also between low and medium RCs. Higher resistance induced higher variances of muscle activity profiles. When cycling only with the left arm, there were significant difference between low and medium and also between low and high RCs and the difference was marginally significant between data obtained in medium and high RCs. In contrast, when cycling only with the right arm, resistance condition did not affect muscle activity variances. Joint angle variances didn't differ significantly for the 3 resistance conditions, neither in bimanual nor in unimanual cycling. Conclusion: the movement is stabilized at kinematic level. To keep this stability when cycling against higher resistance, muscles employ more variable activity patterns. The movement is controlled through stabilizing arm configurations and less by stabilizing muscle activity patterns. The exception is when cycling only by the right arm, the reason of this may be that the central neural control of the dominant arm is so robust that even muscle activity patterns are stabilized and their variance isn't affected by external resistances. Although the left arm's less stable muscle activity patterns affect muscle activity variances of the right arm when cycling bimanually.

Disclosures: **M. Mravcsik:** None. **L. Botzheim:** None. **N. Zentai:** None. **J. Laczko:** None.

Poster

609. Bimanual and Interlimb Control

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Program#/Poster#: 609.07/O42

Topic: D.17. Voluntary Movements

Title: Effects of varying visual feedback on learning a bimanual birhythmic (2:1) isometric force coordination pattern

Authors: M. LEWIS, M. DUNN, E. SHIREMAN, K. MULLER, D. DEAN, Jr, A. CHAUDHARI, N. PATEL, R. T. EAKIN, W. W. SPIRDUSO, *L. D. ABRAHAM; Kinesiology and Hlth. Educ., Univ. Texas Austin, Austin, TX

Abstract: This study replicated a recent unpublished study (Wilson, 2012) which found the bimanual coupling effect was not overcome in a birhythmic isometric force tracking task, unlike the results of Kovacs et al. (2010, 2011) for polyrhythmic bimanual kinematic tasks. Thirty-three right-handed volunteer participants, 13 men and 20 women with a mean age 20.7 (SD = 1.5) years, free from any neurological disorder or physical ailment, were randomly assigned to one of three groups that differed in percent of visual feedback provided during practice trials (100%, fading 50% or 0%). The participants then performed a bimanual birhythmic isometric force tracking task (requiring a 2:1 rhythm between the two index finger forces to move a computer screen cursor with a moving target along a path shaped like a backward C through two complete trips up and back for each trial). The forces required to complete the task were scaled for each participant so that the peak force required for each digit was 30% of that individual's mean maximum voluntary contraction (MVC) digit flexion force, measured at the fingertips. After initial orientation to the apparatus, all participants performed five blocks of five practice trials with the feedback schedule assigned to their group, rested for 30 minutes, then performed an additional five trials as a retention test. During the retention test all groups were provided visual feedback only during the first 12.5% of the task. During practice blocks, the three groups differed in average Root Mean Square Error (RMSE), measured as distance of the cursor from the moving target. The 100% feedback group had consistently low RMSE; the 0% feedback group had consistently high RMSE, and the fading 50% feedback group had steadily increasing RMSE as the visual feedback was reduced across practice blocks. Interestingly, smoothness of the cursor movement, assessed by coefficient of variation of error (CVE) was consistently lower for the 0% feedback group than for the other two groups. Despite these differences between the

groups during the practice trials, no differences occurred between the groups in RMSE or in CVE during the retention block. These results across different schedules of visual feedback during learning support the guidance hypothesis that while performance is enhanced, learning is not optimal when feedback is provided on every trial. These findings also support the position that the bimanual coupling effect in birhythmic isometric force coordination tasks is very strong and cannot be as easily overcome as it is in kinematic bimanual tasks. This may be due in part to the different sensory feedback systems used in isometric force production versus limb movement tasks.

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Poster

609. Bimanual and Interlimb Control

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Topic: D.17. Voluntary Movements

Support: NIH:NICHD R01HD059783

AHA 13CRP14440025

Title: Manual asymmetry during a bilateral reach and hold task

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Abstract: We have previously characterized interlimb and interhemispheric assymetries for unilateral coordination tasks. This work has led to a model of motor lateralization in which one hemisphere is specialized for impedance control that is robust to unstable environmental conditions, while the other hemisphere is specialized for predictive mechanisms that can specify efficient and smooth trajectories under stable environmental conditions. We hypothesize that these two specializations are distributed across the arms during everyday bilateral tasks that involve holding and manipulating, such as when holding a baguette with one hand to slice it with the other hand. We predict that each hand should demonstrate different specializations for each

of these task elements during bilateral behaviors. In order to test this hypothesis, we designed an experimental equivalent of the hold and slice task. In this task, performed in a virtual environment with the unseen arms supported by frictionless air-sleds, the arms are connected by a spring, while one hand maintains its position at the origin of the task, and the other moves to a series of targets distributed across a range of directions. Thereby, the reaching hand is required to take account of the spring load to make smooth and accurate trajectories, while the stabilizer hand must impede the spring load to keep a constant position. Right-handed subjects performed each of two sessions of this task, with the order of the sessions counterbalanced between groups. In one session, the right hand reached while the left hand stabilized, and the second session the left hand reached while the right hand stabilized. Our very preliminary results indicate a hand by task component interaction, such that the right hand showed better reaching performance , with faster and smoother (Jerk) reaching. In contrast, the left hand stabilized better, showing less displacement than the right hand. These findings suggest that the specializations of each cerebral hemisphere for impedance and predictive mechanisms are expressed during bilateral interactive tasks, such as the reach and hold task. To date, this is the first demonstration of the dynamic dominance hypothesis within the context of an asymmetric bilateral task.

Disclosures: E.J. Woytowicz: None. **J. Whitall:** None. **K.P. Westlake:** None. **R.L. Sainburg:** None.

Poster

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Topic: D.17. Voluntary Movements

Support: NSERC

Title: Entrainment of movement kinematics as the default mode of human joint actions: A cooperative grasping study

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Abstract: Humans can be highly effective in coordinating their actions with others. To perform such “joint actions,” the co-actors need to align temporal and spatial aspects of their motor control with great precision. But to study interpersonal coordination most research has

investigated rhythmic limb movements during socially coordinated behaviour with many degrees of freedom in the way the tasks could be performed, and largely the tasks could be performed by one person alone. To probe joint actions affording a maximum amount of cooperation, here we used a task that was irreducible to a single person's actions with low degrees of freedom. We asked two participants at a time to cooperatively grab an object with a precision grasp such that each person used their index and middle fingers of one hand to push from opposite sides of the object and to lift it. As a control condition, we asked the participants to compete in speed as they reached for the opposite sides of the object. We hypothesized that cooperative grasping should yield higher degrees of coordination than competitive reaching, in particular over the course of the experiment. Using infrared motion capture, we recorded the hand movements of 11 pairs of participants. As expected we found that movement coordination for cooperation versus competition became different over time, i.e., towards the end of the experiment, hand velocities were more correlated during cooperative grasping. However, the change came from the competitive condition where correlations started high and declined over time, whereas the cooperative condition showed high correlations throughout. Our data suggest that joint action entrains people's movement kinematics into temporal synchrony, arguably based on forward models that anticipate the movements of the co-actor. Moreover, during competition actors might need to learn to de-synchronize to overcome the default mode of cooperation.

Disclosures: L. Guo: None. **M. Niemeier:** None.

Poster

609. Bimanual and Interlimb Control

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Topic: D.17. Voluntary Movements

Title: Effect of handedness on the generation and execution of upper limb planar movements

Authors: *M. COSCIA[1], E. PIRONDINI[1], N. DUTHILLEUL[2], S. EL KHOURY[3], R. L. DE SOUZA[3], A. BILLARD[3], S. MICERA[1,4];
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Abstract: Handedness is the tendency to prefer the use of a limb in performing motor tasks. Handedness seems result from differences in the neural control of the limbs due to functional and

anatomical asymmetries in the motor cortex, in the corticospinal tract, in the peripheral nervous pathways, in muscle fiber composition, in the motor unit firing rate, and in muscle activity. In this work, we deepen the mechanisms which underlie difference in motor performance on the left and right side by investigating the movement execution, the muscular activity and the force generation in both sides from a group of five right and five left handed subjects while executing motor tasks requiring precision in inter-joint coordination and trajectory formation. The hand dominancy was determined by the Edinburgh inventory test. The subjects executed wide and tight circular movements 8 times clockwise and anticlockwise with no interruptions between repetitions, at comfortable speed, following circles drawn on the center of a table, using at first the dominant and afterwards the non-dominant arm. While performing the motion, subjects held in a tight grip a cylindrical tool whose tip was in contact with the table. The tool included a sensor to measure forces and torques generated at the end-point. Additionally, we recorded upper limb kinematics by placing 29 markers for motion tracking, and the electromyographical (EMG) activity of 15 muscles. The trajectory of the marker in correspondence to the ulnar styloid process, the forces and torques provided by the sensor, and the muscular organization highlighted by muscle synergies obtained factorizing the EMG activity with the non-negative matrix factorization algorithm were compared between sides, and between right and left handed subjects. Our preliminary results showed that right and left handed subjects performed the circular trajectories with different strategies and muscle organization. Muscle synergies were similar between sides during the execution of wide movements; whereas, during the execution of tight movements, the muscle activity of the dominant side required the activation of an additional module compared to the non-dominant side. The results of this work have an important impact from a clinical point of view, as handedness-related differences in movement execution and muscle synergies need to be considered in rehabilitative applications for subjects characterized by motor and muscular asymmetry, such as stroke patients. However, deeper analyses on a larger cohort of subjects are necessary to confirm our preliminary results and to better understand the origin for the handedness-related difference in muscle synergies.

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Poster

609. Bimanual and Interlimb Control

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Topic: D.17. Voluntary Movements

Title: The effects of bilateral reach tasks on postural control in older adults

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Abstract: Many goal-directed behaviors require the coordinated action of both hands which, in older adults, may comprise over 50% of activities of daily living (Killbreath & Heard, 2005). To what extent aging impacts the performance of bilateral tasks is unclear. For example, Stelmach et al. (1988) reported slowing of bilateral reaching movements while Coats & Wann (2012) found that movement time during a bilateral reach, grasp and place task did not vary between older and young adults. Most studies examining bilateral arm function have been performed from a seated position despite recent findings indicating age-related declines in postural control during task-related reaching (Huang and Brown, 2013, 2015). The purpose of this study was to determine the effects of aging and postural configuration on bilateral reaching performance. Fourteen young (mean age 20.6 y) and 16 older adults (mean age 74.4 y) performed unilateral (dominant, non-dominant) and bilateral reaching movements from either a seated or standing postural configuration. Participants reached to illuminated targets located at shoulder and waist heights as fast and as accurately as possible. During the standing condition, participants stood barefoot on a force plate with a shoulder width foot separation. Target-embedded touch sensors recorded movement time. Center of pressure path length was used to assess postural control during the reaching tasks. Postural configuration testing order was counterbalanced in each age group. Postural control demands (i.e. seating vs standing) had no effect on movement duration regardless of reach task (unilateral vs bilateral) in either age group. When reaching from standing, COP excursion increased in both groups during coupled bilateral tasks compared to unilateral reaching. In young adults, COP excursion increased by approximately 30% compared to dominant arm reaching. A much greater effect was seen in older adults where COP excursion increased by over 60% during bilateral tasks. This observation was driven, in part, by greater COP excursions when reaching unilaterally with the non-dominant compared to the dominant arm. In contrast, no arm differences were seen in the young adults. These findings demonstrate that dynamic postural control during bilateral reaching movements is compromised to a larger extent in older adults compared to their young counterparts, possibly due to age-related declines in on-line sensory control of goal-directed movements. Training programs aimed at improving balance control and fall prevention in the elderly should consider the inclusion of goal-directed bilateral reaching tasks, particularly from standing positions.

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Poster

609. Bimanual and Interlimb Control

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Topic: D.17. Voluntary Movements

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Title: The influence of biomechanical constraints on bimanual coordination

Authors: *D. CORDOVA BULENS, F. CREVECOEUR, J.-L. THONNARD, P. LEFÈVRE; Univ. catholique de Louvain, Louvain La Neuve, Belgium

Abstract: Most daily tasks involve bimanual coordination, which in many cases offers redundancy in the way the two limbs can achieve task success. To date, handedness has been considered as the main factor driving bimanual coordination, despite the presence of biomechanical constraints that also induce asymmetries across limbs. For instance, producing a leftward force with one arm will recruit different muscle groups depending on the arm being used. Here we address this issue by showing the impact of these biomechanical constraints on distributed force control. The task consisted in producing a 20 N force using both arms towards visual targets representing the resultant force in the horizontal plane. Visual feedback was provided by mapping the sum of forces applied on the fixed robotic interface onto cursor motion in a virtual reality display (KINARM, BKIN Tech., Kingston, Canada). The force distribution across the two arms was unconstrained and sixteen different directions of force production were tested. We varied the joint configuration to highlight the influence of biomechanics on bimanual control. We modeled this task using human-inspired two-segments upper-limbs acting on the horizontal plane. The two arms are actuated by six groups of muscles, representing mono- and bi-articular flexors and extensors at each joint. The strength of each muscle group was adjusted based on physiological cross-sectional areas of human subjects. The only parameter that varied across simulations, as in the experiment, was the joint configuration, which is expected to impact force production through changes in the Jacobian matrix linking the joint torques to the end-point force. We used a standard optimal feedback control model coupled with positivity constraints on the control variable representing muscles activation. The model predicted that varying the joint configuration should impact the force distribution across the two limbs. Participants' behavior directly supported the model predictions. More specifically, a change in joint configuration modifies the direction of the end-point force produced by each muscle group, therefore modifying the orientation of preferred force direction of each limb. A repeated measures ANOVA confirmed the significant influence of upper-limb configuration on the preferred force

direction of each limb following changes in joint configuration ($F(X,Y) = 36.23$, $p<0.001$). These results emphasize that the nervous system distributes control across the two limbs while taking upper-limb geometry into account. We conclude that biomechanical constraints are an important factor for understanding how the nervous system performs bimanual control.

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Poster

609. Bimanual and Interlimb Control

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Topic: D.17. Voluntary Movements

Title: Different levels of intracortical inhibition are involved in bimanual common vs. dual-goal tasks and related to interlimb interaction

Authors: *W.-W. LIAO[1], J. WHITALL[1,2], J. BARTON[1,3], S. MCCOMBE WALLER[1]; [1]Physical Therapy and Rehabil. Sci., Univ. of Maryland Baltimore, Baltimore, MD; [2]Fac. of Hlth. Sci., Southampton, United Kingdom; [3]Dept. of Neurol., Univ. of Maryland, Baltimore, MD

Abstract: Individuals following stroke have exhibited various degrees of deficits in both paretic and non-paretic arms. Nevertheless, the majority of activities of daily living require collaboration between the arms. Some tasks involve a common-goal in which two arms sharing a single focus, such as pulling out a drawer with both arms. Others involve similar but separate goals for each arm, such as picking up different items with each arm separately. The ability to restore function of both arms in bimanual tasks is crucial for stroke survivors to achieve independent living. We hypothesize that different cortical control parameters are involved in bimanual common versus dual-goal tasks, and that this difference will be demonstrated in interlimb performance interaction as well. In this pilot we determine intracortical inhibition and its relationship to interlimb interaction in bimanual common-goal vs. dual-goal isometric force tasks in young non-disabled adults. Subjects: Eight right-handed subjects. Methods: Isometric force tasks with visual feedback were undertaken in three conditions: unimanual, bimanual dual goals for each arm and bimanual common-goal for both arms. Force production of each arm during 10% submaximal tasks and intracortical inhibition (SICI) of both hemispheres for biceps were evaluated during the three conditions. Results: A significant reduction of SICI was found in both bimanual tasks compared to the unimanual tasks ($p<.05$) in dominant hemispheres, with a trend toward greater reduction in dual-than common-goal tasks ($p=.06$). Both bimanual tasks showed less intracortical

inhibition compared to unimanual tasks in non-dominant hemispheres, but only dual-goal tasks reach a statistically significant difference ($p<.05$). A significant relationship was found between the difference of force variability of each arm and total motor output (the sum of force during bimanual contractions) in common but not dual-goal tasks based on a linear regression model ($p<.05$, $R2= .805$). Conclusion: Bimanual common and dual-goal tasks could release both hemispheres from mutual inhibition. The levels of SICI within and between hemispheres as well as force organization pattern were different in common- vs. dual-goal tasks, and this may suggest that these two tasks were modulated by potentially different inhibitory cortical parameters. Our findings indicate that task specific training might be needed for different types of bimanual tasks in healthy as well as patients with neurological disorder.

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Poster

609. Bimanual and Interlimb Control

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Topic: D.17. Voluntary Movements

Title: Effects of task constraints bimanual coordination in patients post-stroke

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Abstract: Coordination during goal-directed movements emerges from an interaction of task and individual constraints. In this study, we investigated the effects of two task constraints on bimanual coordination in patients with stroke and age-matched controls. Two specific task constraints were manipulated: symmetry and angular displacement. The goal of the bimanual task was to cooperatively use two hands to move a virtual block in to a goal window. Symmetry was manipulated along two dimensions: symmetric and asymmetric. During symmetric task, two hands reached forward to cause upward displacement of the virtual block. During the asymmetric task, the upward movement of the block resulted from one hand reaching forward and the other pulling backward. During standard angle condition, the angle of the block changed dependent on the displacement of the two hands relative to the starting position. In the fixed angle condition, the virtual block was locked in a horizontal position and did not depend on the displacement of the two hands relative to the starting position. Bimanual coordination was determined using two separate analyses: individual contribution of the two hands and cross-correlation. Cross-correlation analyses yielded a cross-correlation coefficient and time-lag. During the symmetric

task, control participants moved the two hands equally during both standard and fixed angular positions. In contrast, patients demonstrated reduced movements of the paretic arm during the fixed angular condition, but not the standard angle condition. During the asymmetric task, there was a differential effect of the angular displacement. In the fixed angle asymmetric condition, control participants demonstrated different displacements of the two arms: the pulling hand had significantly greater excursions compared to the reach hand, irrespective of the dominance. This suggests that biomechanical factors play an important role in control and coordination of bimanual movements. In patients with stroke, however, the paretic arm showed reduced excursion irrespective of the action (reaching or pulling) required. During the standard angle asymmetric condition, the relative contributions of the two arms were restored to being almost equal, thus providing evidence that task constraints can be manipulated to improve bimanual coordination in patients with stroke.

Disclosures: R.L. McGrath: None. **S.S. Kantak:** None.

Poster

609. Bimanual and Interlimb Control

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Topic: D.17. Voluntary Movements

Title: Multi-frequency bimanual force production: symmetric and asymmetric interference

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Abstract: Results from a recent experiment (Kennedy et al., 2015) indicated consistent and identifiable distortion of the left limb forces that could be attributable to the production of right limb forces during a multi-frequency bimanual force task. However, distortions in the forces produced by the right limb that could be attributable to the production of force in the left limb were not observed. The present experiment was designed to determine whether an increase in the force requirements for one limb would result in an increase in the interference observed in the contralateral limb and to determine if the strength of the interference was influenced by the limb performing the higher force and/or frequency. Participants (N=40) were required to rhythmically coordinate a pattern of isometric forces in a 1:2 or 2:1 coordination pattern. The 1:2 task required the right limb to perform the faster frequency while the 2:1 task required the left limb to perform the faster frequency. In each task (1:2, 2:1) participants were also randomly assigned to a force condition in which the left or right limb was required to produce a force pattern of 5 N while the

contralateral limb was required to produce a 5N, 15N, and 25N force pattern. Each participant performed 13 practice trials and 1 test trial per force level. Lissajous displays were provided to guide performance. The results indicated that the right limb influenced the left limb regardless of force level, loading condition, or frequency assignment in both the 1:2 and 2:1 tasks. However, the left limb only appeared to influence the right limb when assigned the faster frequency. This result is consistent with the notion that neural crosstalk is asymmetric with the dominant hemisphere exerting a stronger influence on the non-dominant limb than the non-dominant hemisphere does on the dominant limb.

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Poster

609. Bimanual and Interlimb Control

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Topic: D.17. Voluntary Movements

Title: Mirror training augments the cross-education of strength and reduces the contralateral silent period duration in the untrained but not the trained wrist

Authors: *T. ZULT[1], S. GOODALL[2], K. THOMAS[2], S. SOLNIK[3,4], T. HORTOBÁGYI[1,2], G. HOWATSON[2,5];
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Abstract: Introduction: Unilateral resistance training strengthens the actively contracting muscles and also the homologous muscles on the untrained side – a phenomenon called cross-education. The increased neural drive from the untrained primary motor cortex (M1) to the transfer muscles is thought to contribute to cross-education, but also intracortical paths seem to play a role. The magnitude of cross-education is modest, however, it has been hypothesized that mirror-viewing of the exercising hand can augment cross-education by modulating intracortical and corticospinal paths. Consequently, we examined the idea that mirror training augments the cross-education of strength by modifying corticospinal excitability (CSE) and short-interval intracortical inhibition (SICI) of the untrained M1 and contralateral silent period (cSP) duration recorded from the right-trained and left-untrained flexor carpi radialis (FCR). **Methods:** Healthy, young right-handed adults, were allocated to a mirror (N = 11) and no-mirror training group (N =

12) and performed 640 right wrist flexions (contraction speed: 20°/s) at 80% maximal voluntary contraction (MVC) during 15 sessions over three weeks. Pre- and post-test neurophysiological measurements were performed. CSE and SICI of the right-untrained M1 were measured during right wrist flexion in a mirror and no-mirror condition. The cSP was only measured in the no-mirror condition during isometric wrist flexion. All contractions were performed at 60% pre-test MVC and 60% absolute MVC. **Results:** MVC of the trained wrist increased equally in the mirror (71%) and no-mirror groups (73%; $P = 0.961$). MVC of the untrained wrist improved more in the mirror (61%) than no-mirror group (34%; $P = 0.047$). A 16% reduction in the untrained FCR's cSP duration was observed for the mirror group, while the no-mirror group showed a 12% increase ($P = 0.008$) when measured at 60% pre-test MVC (15% decrease vs. 8% increase when measured at 60% absolute MVC; $P = 0.030$). No changes in the trained FCR's cSP duration were found ($P > 0.05$). CSE increased and SICI decreased across groups for the no-mirror and mirror condition at 60% absolute MVC, while no changes were observed at 60% pre-test MVC. **Discussion:** Augmented sensory feedback by mirror-viewing the exercising hand increases cross-education by reducing the $GABA_B$ mediated cSP duration. CSE and $GABA_A$ mediated SICI of the untrained M1 were modified by the strength training itself, but were not additionally affected by mirror training. Although there is the suggestion that $GABA_B$ receptor function affected cross-education, it is conceivable that other neural circuits are implicated that we did not measure.

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Poster

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Topic: D.17. Voluntary Movements

Support: MRC NIRG, MR/K023012/1

Title: Crossed reflexes in distal muscles in the upper limb

Authors: *D. S. SOTEROPOULOS;
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Abstract: In response to a mechanical perturbation, stretched muscles produce a burst of muscle activity, typically composed of multiple components (mediated by multiple pathways). During

bimanual movements, a response can be seen in the opposite, and unperturbed limb. Such crossed reflexes have been rarely studied for more distal movements involving finger muscles. We examined crossed reflexes for an intrinsic hand muscle, the first dorsal interosseous (1DI), to assess if finger muscles show crossed responses to unilateral stretch, and if yes, how these responses depend on the perturbation parameters of the opposite hand. Subjects performed a bimanual finger abduction task with the left finger performing an isometric contraction and the right finger an isotonic contraction. Force and position signals were collected from the left and right manipulanda respectively, and these were used to control the position of a cursor on a visual display. The task required subjects to move the cursor from a starting position to a target position following an audio-visual cue, and hold in target for ~1.5s. Feedback was given at the end of the trial on their performance. The cursor could only be moved in the horizontal direction, and its position was determined by an average of the left and right finger signals. On some trials a perturbation was given to the right finger in a clockwise or anticlockwise direction (randomly chosen). Muscle activity was recorded from 1DI bilaterally during the task. Analysis was carried out on the rectified muscle activity (EMG) aligned to perturbation onset. Subjects were able to carry out the task successfully, scoring >95% on trials with no perturbations. Most subjects (9/11) showed a response in the left (unperturbed) 1DI with an onset latency <100ms. The crossed response had two components - an early inhibitory one (mean onset latency 56ms) and a later excitatory component (mean onset latency 83ms). The peak amplitude of these responses relative to the baseline EMG levels varied from subject to subject and ranged from -40% to -15% (mean -25%) for the early suppression, and 5% to 43% (mean 25%) for the later facilitation. The crossed response depended on the direction of the perturbation- a clockwise perturbation of the R1DI produced much less suppression in the L1DI compared to the anticlockwise perturbation (-25% vs -13%, anticlockwise vs clockwise). The inverse was seen for the later crossed component (12% vs 25%, anticlockwise vs clockwise). Our results show that intrinsic finger muscles can show long latency responses to a stretch in the opposite finger, and that these responses depend on the parameters of the perturbation given to the opposite finger.

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Poster

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Title: Bilateral movement time delays when reaching and grasping one or two objects

Authors: *Y. LEI[1], F. CALABRO[2], M. PEREZ[1,2];
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Abstract: Most of our daily tasks involve reaching and grasping movements with the arms. However, the extent to which motion of one arm affects movement of the contralateral arm remains poorly understood. Using kinematics analysis we measured arm acceleration (time between movement onset and peak arm velocity), hand opening (time between hand opening onset and maximum aperture size between the index finger and thumb) and closing (time between the maximum aperture size and grasp) during unilateral and bilateral self-paced and ballistic reach-to-grasp movements of one or two small and large cylinders in healthy controls. We found that when reaching for a single object, the time to close the hand was largely increased during bilateral compared to unilateral trials, regardless of the object and movement speed tested. Whereas, arm acceleration and hand opening times remained similar across trials. Notably, bilateral movement time delays were present at different phases of the reach-to-grasp movement when reaching for two objects. Here, arm acceleration time remained similar but the time to open and close the hand progressively increased during bilateral compared with unilateral movements, regardless of the object and movement speed tested. Our findings indicate that extrinsic (object size) and intrinsic (movement speed) variables influence the grasping but not the arm acceleration phase of the reach-to-grasp task, consistent with the view that demands for precise control during grasping gradually increases when approaching the object. We argue that the distribution of the bilateral movement time delays during reach-to-grasp are object-directed.

Disclosures: Y. Lei: None. **F. Calabro:** None. **M. Perez:** None.

Poster

610. Stroke: Impairments and Recovery

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 610.01/P6

Topic: D.17. Voluntary Movements

Support: 1R56NS070879

R21 HD067906-01A1

Title: Neuronal substrate supporting hand function in chronic stroke patients with incomplete motor recovery

Authors: *J. J. FREEMAN[1], K. P. REVILL[1], M. W. HAUT[2], G. M. KOWALSKI[1], M. WISCHNEWSKI[1], S. R. BELAGAJE[1], F. NAHAB[1], D. J. COBIA[3], X. HU[1], G. HOBBS[2], C. M. BUETEFISCH[1];
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Abstract: Ischemic stroke often impacts the integrity of the primary motor cortex (M1) and its corticospinal projections (CST) resulting in incomplete recovery of hand function. The neural substrate supporting compromised hand function in the chronic phase of stroke is not well understood. Here we determine in chronic stroke patients the relationship between hand function and reorganization of ipsilesional M1 and CST. Sixteen patients (64.37±9.21 yr.) with incomplete recovery from stroke (>6 months) involving M1 or/and CST participated in the study. Their affected hand was functionally impaired as demonstrated by the higher scores on Jebsen- Taylor Test ($t(15)=7.668$, $p< .0001$) and of limited use in activities of daily living (Motor Activity Log score 1.05±1.03, scale 0-5, lower score = less use). In all patients M1 and CST structure and function were determined using magnetic resonance imaging (MRI) and transcranial magnetic stimulation (TMS). An input-output curve of the ipsilesional M1 hand area was acquired with TMS. A Boltzmann sigmoidal function was fitted to extract maximum motor evoked potential amplitude (MEPmax), inflection point (S50), and slope-parameter. M1 intracortical inhibition was measured using paired pulse TMS. TMS measures of stroke patients were compared to 11 age-matched, healthy subjects. For measures of M1 structure, the distance between representations of the gray-white boundary and pial surface was calculated. These measures were then applied to a standard atlas to extract M1 cortical thickness (FreeSurfer). For CST fractional anisotropy (FA) measures, TRACULA within FreeSurfer was used. We found that in patients, MEPmax and S50 were lower when compared to healthy subjects (MEPmax:$t(25)=23.28$ $p< .0001$; S50:$t(25)=3.88$, $p = .0007$) indicating that maximum CST output was reduced and excitability of surviving M1 neurons increased. Further, in patients, there was a trend towards reduced M1 intracortical inhibition which did not reach statistical significance. TMS measures correlated with mean ipsilesional M1 volume (maxMEP ($r= -.502$, $p = .04$); S50 ($r= .489$ $p = .045$); and SICI ($r = -.054$ $p = .0453$)). There was no significant correlation between hand function (Jebsen Taylor Test score) and any of the TMS or MRI measures of ipsilesional CST or M1. In contrast, impaired hand function correlated with greater

FA values of contralesional CST (r = .666, p = .025). In conclusions, the lack of strong correlations between hand function and measures of ipsilesional M1 and CST reorganization indicates that compromised hand function in the chronic stroke patients likely depends on additional brain areas, possibly involving the contralesional hemisphere.

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Poster

610. Stroke: Impairments and Recovery

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Program#/Poster#: 610.02/P7

Topic: D.17. Voluntary Movements

Support: NIH Grant T32 GM081741-06

NIH CoBRE P20GM109098

Title: The relationship between muscle synergies and limb dynamics is altered after a stroke

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Abstract: Stroke is the leading cause of adult disability in the United States and second globally. Persistent post-stroke movement disorders affect nearly one third of all individuals who suffer from a stroke. It is known that motor deficits in stroke survivors are linked to altered muscle activation patterns. Current theories of motor control postulate that the nervous system produces the normal repertoire of movements by combining several muscle synergies that represent basic units of control. Here we sought to investigate how changes in muscle synergies post-stroke relate to changes in limb dynamics that accompany arm motor impairment. Stroke patients were recruited to perform a set of twenty-eight reaching tasks with both their paretic and non-paretic arm. Center-out reaching tasks were presented in horizontal and vertical planes using a virtual reality headset (Oculus Rift). Movements were performed in three dimensions without external constraints other than the instruction not to move the wrist. Muscle activity from twelve muscles of the arm that span shoulder, elbow, and wrist joints were recorded during the movements synchronously with motion capture. Joint angles, angular velocity, and torques for shoulder, elbow, and wrist joints were calculated from the motion capture data. To examine the

relationship between muscle activity and limb dynamics, non-negative matrix factorization (NNMF) was used to extract synergies from both kinematic-dynamic data and EMG data. The kinematic-dynamic data set included joint angles, velocity and torques subdivided into gravitational and inertial components for all twenty-eight movements. Joint torques were further subdivided into flexion and extension components to create non-negative profiles of limb dynamics suitable for NNMF analysis. Resulting synergies from the kinematic-dynamic decomposition were then compared to each of the synergies extracted from the EMG data using cross-correlation analysis. Results indicate that the relationship between certain EMG synergies and kinematic-dynamic synergies is reduced post-stroke compared to that of healthy individuals. This suggests that stroke disrupts the assembly of specific motor synergies, which causes unique patterns of motor impairment.

Disclosures: E.V. Olesh: None. **V. Gritsenko:** None.

Poster

610. Stroke: Impairments and Recovery

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 610.03/P8

Topic: D.17. Voluntary Movements

Support: The Brinson Foundation

Title: Altered spatial muscle activation patterns reveal possible mechanisms of motor impairment in stroke

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Abstract: We investigated the spatial electromyogram (EMG) patterns using the high density grid electrodes to explore possible mechanisms of motor impairment in stroke survivors. The study was focused on spatial analysis of the high density EMG data where we transformed the conventional time-domain EMG data into spatial root man square (RMS) maps. We recorded EMG data from the muscle biceps bachii during sustained, non-fatiguing, voluntary contraction at various force levels using 128-channel grid electrodes arrange in two 16x4 grids covering both the long and the short heads. The EMG data was processed and RMS values were calculated over the total length of signal (5 sec) for each channel. Thus we calculated spatial maps of muscle activity (EMG signal) from both affected and contralateral sides at various force levels.

We calculated EMG spatial maps and their normalized (to the maximum RMS within the map) maps for five different force levels (20%, 30%, ⋯, 60% of the maximum voluntary contraction). We found significant differences between the spatial distributions of normalized RMS maps of both sides (affected vs contralateral arm) at all force levels. However, no such differences were observed in healthy control group. We postulate that multiple mechanisms can cause the altered spatial patterns in stroke survivors. The altered neural control as a result of lesion (and later on due to neuroplasticity) is probably the leading cause of the observed differences. We assume that a snapshot of the average electrical activity over the whole muscle provides important information about the neural control of the muscle. A changed spatial pattern of the activity can directly result from an altered neural control where some parts of the muscle are no more used for force generation (at any force level). Such a phenomenon may results into muscle atrophy or at the worst motor unit death. A correct identification of such mechanisms of motor impairment is crucial for developing intervention therapies.

Disclosures: **G. Rasool:** None. **B. Afsharipour:** None. **N.L. Suresh:** None. **X. Hu:** None. **W.Z. Rymer:** None.

Poster

610. Stroke: Impairments and Recovery

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 610.04/P9

Topic: D.17. Voluntary Movements

Title: Reconstructing the three-dimensional ultrasound elastography of human biceps muscle

Authors: ***X. HU**[1], A. LAI[2], M. DUFF[2], N. L. SURESH[2], W. Z. RYMER[2];
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Abstract: Quantifying the mechanical properties (e.g., elasticity) of skeletal muscle *in vivo* can be helpful in understanding the tissue characteristics of the muscle in both intact and pathological conditions. Shear wave elastography is a promising technique that can quantify tissue elasticity noninvasively. The objective of this study was to reconstruct the three-dimensional spatial features of the elasticity in human biceps muscle. Using dense scans of two-dimensional ultrasound shear wave imaging of the biceps muscle combined with spatial tracking of the upper limb and the ultrasound probe, we reconstructed the three-dimensional elasticity estimates of the biceps muscle. Such information potentially provides us with a non-invasive and low-cost tool to assess the spatial features, such as the homogeneity, of the muscle elasticity, which can be used for clinical diagnosis and treatment assessment.

Disclosures: **X. Hu:** None. **A. Lai:** None. **M. Duff:** None. **N.L. Suresh:** None. **W.Z. Rymer:** None.

Poster

610. Stroke: Impairments and Recovery

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Program#/Poster#: 610.05/P10

Topic: D.17. Voluntary Movements

Title: Effects of wrist tendon vibration on cortical activity during arm stabilization

Authors: *D. B. SNYDER, S. A. BEARDSLEY, B. D. SCHMIT;
Marquette Univ., Milwaukee, WI

Abstract: Artificial activation of sensory afferents by way of wrist tendon vibrations (TV) has been shown to improve end point stabilization in neurologically intact and post stroke populations. This improvement in the ability to stabilize may be due to enhanced sensorimotor integration within cortical networks. In the work presented here, we use electroencephalography (EEG) and electromyography (EMG) together with goal directed stabilization tasks to examine if cortical changes contribute to enhanced end point stabilization during TV. Ten healthy controls performed a series of 2D reach and hold tasks using a passive arm support system (recording limb position) to control a cursor projected onto a horizontal display. Each task condition consisted of a point to point movement to a target followed by a 4 second stabilization period with either no perturbations, perturbations, or perturbations and TV. TV (70 Hz) was applied to the forearm wrist musculature. EEG data were recorded using a 64 channel electrode system, bandpass filtered from 0.1 to 100 Hz, notch filtered at 70 Hz, amplified and processed using independent component analysis to remove artifacts. EMG data were recorded from the flexor carpi radialis, extensor carpi ulnaris, biceps, lateral head of the triceps, and the anterior and posterior deltoid, bandpass filtered from 10 to 350 Hz, notch filtered at 70 Hz, amplified by 1000, root-mean squared (100 ms window) and normalized to their respective maximum voluntary contraction. MATLAB was used for all data analysis. Time courses and source localizations of Beta band (13 - 26 Hz) and Gamma band (27 - 50 Hz) power were computed from EEG data to examine the spatiotemporal aspect of cortical activity. Time course and source localization results of conditions with TV and following TV showed an increase in Beta band event related desynchronization (ERD) compared to conditions pre-TV. Analysis of the TV condition revealed higher Gamma band power in the sensorimotor cortex contralateral to the arm

being moved. These results suggest TV enhances sensorimotor integration resulting in enhanced end point stability.

Disclosures: D.B. Snyder: None. **S.A. Beardsley:** None. **B.D. Schmit:** None.

Poster

610. Stroke: Impairments and Recovery

Location: Hall A

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Program#/Poster#: 610.06/P11

Topic: D.17. Voluntary Movements

Support: Canadian Partnership for Stroke Recovery

Title: Condition-specific deficits in intersegmental coordination after stroke

Authors: *K. SAMBASIVAN[1,3], K. HAENTJENS[2], S. KHANAFER[4], S. K. SUBRAMANIAN[6,3], M. C. BANIÑA[3], A. G. FELDMAN[6], H. SVEISTRUP[5,7], M. F. LEVIN[1,3]; [1]Sch. of Physical and Occup. Therapy, [2]Dept. of Neurosci., McGill Univ., Montreal, QC, Canada; [3]Feil-Oberfeld Res. Ctr., Jewish Rehabil. Hospital, Ctr. for Interdisciplinary Res. in Rehabil. of Greater Montreal (CRIR), Laval, QC, Canada; [4]Sch. of Human Kinetics, [5]Sch. of Rehabil. Sci., Univ. of Ottawa, Ottawa, ON, Canada; [6]Dept. de Neurosciences, Univ. de Montréal, Montreal, QC, Canada; [7]Elisabeth Bruyere Hosp., Ottawa, ON, Canada

Abstract: Stroke leads to deficits such as weakness, spasticity and incoordination affecting upper-limb reaching. Reaching is also affected by stroke-related postural control problems characterised by an increase in lateral deviations of the centre of pressure (evaluated with Limits of Stability (LoS) index). Deficits in the coordination of a redundant number of degrees-of-freedom (DFs) of the body (excess DFs), may also affect reaching. We characterised reaching ability of both arms, with and without the involvement of additional trunk DFs in patients with chronic stroke (18-75yrs; Fugl-Meyer Assessment (FMA): 54.0±12.5/66; Reaching Performance Scale for Stroke (RPSS): near=15.6±2.9/18; far=15.7±3.0/18 target) and Chedoke Arm and Hand Activity Inventory (CAHAI): 47.4±12.8/63) compared to healthy age-matched controls. Kinematics of two arm tasks involving a target located at 66% arm length were recorded in seated subjects without vision: stationary-task (maintaining finger above target) and reaching-task, while leaning the trunk forward (total of 40 trials). For each task, in 40% of trials, trunk movement was unexpectedly blocked such that movements were made with and without trunk involvement. LoS in sitting was measured in 8 directions separated by 45° intervals using a force-plate. The primary outcome measures were gain (G) for stationary-task defined as the degree to

which the potential contribution of trunk displacement to hand motion was compensated by appropriate changes in arm DFs (G=1: complete compensation, G=0: no compensation); and endpoint position difference in reaching-task. Comparisons were made with Mann-Whitney U tests. Clinical measures and LoS area were correlated with primary outcomes. G of more-affected arms was lower (G=0.49±0.19) compared to less-affected arms (G=0.69±0.14; U=20.5, p=0.02) and controls (G=0.74±0.16; U=7.00, p=0.04). There was no correlation between the more-affected arm G and FMA, CAHAI, LoS area. Endpoint position differences were similar between groups but those of the more-affected arms correlated with FMA (r=-0.76), RPSS (near: r=-0.85, far: r=-0.87) and LoS area (r=0.71). Stroke affects the ability to compensate for additional trunk movement when the hand is held stationary. During reaching, excessive trunk movement compensates for deficits in upper limb motor function. Patients with stroke have deficits in condition-specific adjustment of intersegmental coordination. Understanding motor control deficits in managing redundant DFs will help clinicians develop targeted interventions to improve upper limb reaching ability in individuals with stroke.

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Poster

610. Stroke: Impairments and Recovery

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Topic: D.17. Voluntary Movements

Support: CHRP

REPAR-OPPQ

OPPQ

CPA

Title: Temporal and spatial upper-limb interjoint coordination in chronic stroke subjects versus healthy individuals when reaching

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Abstract: Movement coordination which plays a major role in upper-limb(UL) function is commonly affected after stroke. We assessed UL interjoint coordination (IJC) deficits in people with stroke compared to age- and gender-matched healthy subjects and the influence of these deficits on the performance of a simple reaching task. UL kinematics were recorded using 28 markers on the arm, trunk, nose and target (Optotrak, 30s, 100Hz). Two trials of 10 movements each in which subjects (n=20) alternatively touched their nose and a target (ReachIn; ReachOut) located at 90% arm-length, as fast as possible were recorded for each arm. Healthy subjects (n=20) made the same reaching movementsat self-paced and slow speeds to match speeds of stroke subjects. Data for movements in each direction were analyzed to determine relationships between time to perform the task and arm and trunk kinematics. The relationships between temporal and spatial IJC kinematic measures and clinical scores were determined.Compared to healthy subjects, stroke subjects made more curved endpoint trajectories (Index of curvature: stroke=1.23, control=1.04, $p < 0.05$, ReachIn) and used less shoulder horizontal abduction (stroke=11.8º, control=17.6º, $p < 0.001$, ReachIn).Stroke subjects moved their affected arm slower than their less-affected arm (ReachIn: 18%, ReachOut: 43%; for both directions $F=14.136$, $p<0.001$) and had more curved trajectories (ReachIn: 18%, ReachOut: 27%; for both directions $F=6.003$, $p<0.05$).Interjoint coordination was similar between the two arms. Stroke severity was moderately correlated with endpoint speed ($r=-0.55$, $p=0.006$) and straightness ($r=-0.47$, $p=0.018$) but not precision. Time to perform the task correlated with endpoint straightness ($r=0.77$, $p=0.001$), temporal ($r=0.63$) and spatial ($r=-0.61$) interjoint coordination. Shoulder horizontal abduction range ($\beta=0.127$), temporal ($\beta=0.855$) and spatial ($\beta=-0.191$) interjoint coordination explained 82% of the variance in the time to perform the task. Shoulder movement and temporal and spatial interjoint coordination were predictive of the time to perform the task, indicating the influence of UL joint configuration limitation for the performance of reaching movements after stroke.

Disclosures: **M.R.M. Rodrigues:** None. **M. Slimovitch:** None. **A.K. Blanchette:** None. **M.F. Levin:** None.

Poster

610. Stroke: Impairments and Recovery

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Topic: D.17. Voluntary Movements

Support: Heart and Stroke Foundation Centre for Stroke Recovery

Natural Sciences and Engineering Research Council of Canada

Title: Corticospinal resetting of the threshold (referent) position for activation of muscles during motion at the elbow joint

Authors: *S. K. SUBRAMANIAN[1,2], L. RODRIGUES[2,3], L. RYCKEMBUSCH[2,3], T. BROHMAN[2,4], D. BARTHELEMY[2,5], M. F. LEVIN[2,6], A. G. FELDMAN[1,2];
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Abstract: Muscles become active when the actual position of body segments deviates from their threshold positions. Threshold positions represent the origin of the spatial frame of reference (FR) for muscle action. The level of muscle activity depends on the difference between the actual and threshold body segment positions. Voluntary motor actions result from central shifts in the threshold position, thus shifting the FR. It has been shown that the corticospinal (CS) system is involved in threshold position resetting underlying motion at the wrist joint. We investigated whether or not the CS system accomplishes threshold position resetting at the elbow joint. We also investigated how injury affecting the CS tract influences threshold position resetting. Subjects with upper limb hemiparesis after stroke (Fugl-Meyer scores: 20-65/66) and two groups of healthy controls (young: aged 20-35) and older (age-matched to the stroke group) participated in the study. All subjects voluntarily moved their elbow joint from an initial flexed to a final extended position and vice-versa for a total of 30 trials. CS influences at both positions were measured using MEPs elicited by transcranial magnetic stimulation to the biceps site in the contralateral motor cortex. Passive elbow muscle forces were compensated with an elastic band such that elbow muscle activity was approximately equalized at the two positions. Muscle activity was recorded from two elbow flexors (biceps brachii and brachioradialis) and extensors (lateral and medial heads of triceps brachii). Although the EMG activity of elbow muscles was similar, CS influences were different at the two positions. In the healthy groups, flexor MEPs were greater in the elbow flexion than the extension position and vice versa for extensors (reciprocal pattern). Similar patterns were observed only in a subgroup of patients. In the remaining patients, the pattern was either absent or reversed. Results support the notion that CS system participates in threshold position resetting underlying active motion and that this capacity may be affected by stroke. Results also reinforce previous findings suggesting that the motor cortex controls motor actions by shifting spatial FRs. Deficits in shifting spatial FRs may underlie motor deficits in stroke.

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Poster

610. Stroke: Impairments and Recovery

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Topic: D.17. Voluntary Movements

Support: CIHR Grant

Title: Residual deficits in arm coordination in an obstacle avoidance reaching task in individuals with good arm recovery after stroke

Authors: ***M. C. BANINA**[1,2], M. F. LEVIN[1,2];
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Abstract: After stroke, 40-78% of individuals recover a good amount of arm function. Clinical evaluation of these individuals demonstrates that arm function falls within normal physiological limits. Based on their high level of recovery, these individuals should not have any major activity limitations, yet many studies have shown that well recovered people after stroke do not use their arm to the expected amount in everyday life activities. Decreased use may be associated with undetected motor deficits only identifiable when individuals attempt higher order tasks requiring complex coordination and quick changes in movement. One higher order motor task, obstacle avoidance (ObAv) while reaching, commonly occurs in everyday environments but is not routinely assessed by clinical scales. We hypothesized that well recovered people after stroke would have altered arm coordination and poor performance in an ObAv reaching task compared to healthy controls. A virtual environment (VE) was developed simulating a refrigerator with 2 sliding glass doors stocked with bottles on 2 shelves. Subjects reached as fast as possible with their affected/dominant arm into the refrigerator and retrieved a bottle (unobstructed reach, U). In random trials (RAND, 30% of 60 trials), the door ipsilateral to the reaching arm closed soon after reach initiation and partially obstructed the bottle (Ob trials). Subjects were instructed to retrieve the bottle without the hand/arm hitting the door. Arm and trunk movements were recorded with 24 active markers by an Optotrak system. Overall success rates, task performance and movement quality variables for U, successful avoidance (ObS) and failed avoidance (ObF) trials were recorded. Mean endpoint phase plots of ObS and ObF were overlaid on U and divergence points between the plots were determined (DP=% of reach distance). In RAND, at a

success level of 65%, the proportion of subjects who achieved success was significantly lower for the stroke group (12%) compared to controls (42%; $z=1.85$, $p<0.05$). For both groups, U reaching was similar and ObS was characterized by DP occurring closer to the starting position (Ctrl: DPS=11±6%, DPF=33±38%, $p<0.05$; Stroke: DPS=23±17%, DPF=65±33%, $p<0.05$). However, the margin of error in the stroke group was about half that of the controls. In addition, stroke subjects used altered shoulder/elbow coordination patterns compared to controls to successfully avoid the door. Stroke subjects had residual movement deficits that were revealed through a challenging motor task. The potential of using challenging UL tasks to identify higher order motor control deficits should be considered when assessing post-stroke motor recovery.

Disclosures: M.C. Banina: None. **M.F. Levin:** None.

Poster

610. Stroke: Impairments and Recovery

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European Research Council Advanced Grant DEMOVE No. 267888

Title: Motor unit coherence among muscles of the flexion synergy in individuals with chronic hemiparetic stroke

Authors: *L. C. MILLER[1,2], F. NEGRO[3], C. HECKMAN[1], D. FARINA[3], J. P. A. DEWALD[1]; [1]Northwestern Univ., Chicago, IL; [2]Florida Intl. Univ., Miami, FL; [3]Univ. Med. Ctr. Gottingen, Gottingen, Germany

Abstract: For individuals with chronic hemiparetic stroke with moderate-to-severe motor impairment, movement of the paretic upper limb is typically constrained to an abnormal muscle co-activation pattern of shoulder abductors and elbow, wrist, and finger flexors. This pattern is described clinically as the flexion synergy (FS), and it is postulated to be due to an increased influence of the anatomically diffuse reticulospinal tract following stroke-induced corticospinal

tract damage. Coherence among motor unit (MU) discharge is used to determine the frequencies at which motor units are co-modulated, particularly when it is calculated on cumulative spike trains composed of multiple concurrently active MUs rather than MU pairs. Previous studies in humans examining EMG coherence in bilateral arm muscles during startle (Grosse & Brown, 2003) and in neck muscles (Blouin et al, 2007) have suggested that the low-beta frequency band (~10-20 Hz) may reflect reticulospinal drive. The goal of the study was to examine coherence among cumulative MU spike trains from deltoid (DELT), biceps (BIC), and finger flexors (FF) of post-stroke individuals during shoulder abduction (SABD) to explore the frequencies at which coherence appears in muscles of the FS. 6 post-stroke participants with moderate-to-severe impairment and 2 control participants completed the study. The forearm of seated participants was casted to a device capable of measuring isometric shoulder, elbow, wrist, and finger torques simultaneously. 64-channel surface EMG grids were placed on DELT, BIC, and FF. Signals were decomposed into MUs using the Convolution Kernel Compensation technique. Participants performed 2-6 isometric SABD trials at 10%, 25%, and 40% of maximum voluntary torque. For this preliminary analysis, coherence spectra were pooled across all torque levels for each participant group. Pooled spectra were z-transformed and baseline corrected to enable comparison between groups. During SABD, the paretic arm of the post-stroke participants generated substantial elbow and finger flexion torques consistent with FS expression. Participants in the control group did not generate appreciable elbow or finger torques, but MU could be extracted from BIC and FF due to activity related to postural stabilization. In the control group, there was little-to-no significant coherence in the beta band of DELT, BIC, or FF, but significant peaks emerged in the stroke group in all muscles. These preliminary results support the hypothesis of an increased influence of reticulospinal motor pathways in the upper limb following stroke.

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Poster

610. Stroke: Impairments and Recovery

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Topic: D.17. Voluntary Movements

Title: A computational approach to understand a valley of motor recovery

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Abstract: Improvements in functional performance following a brain lesion can result either from compensation or from true recovery of normative movements. Because compensation can ultimately impede recovery, it is desirable to promote true recovery of normative movements. However, patients are often "trapped" in producing the less effective compensatory movements. What are the computational principles underlying this difficulty in transitioning from compensatory to normative movements? Here, we considered a computational model of neuro-rehabilitation based on Han et al. (2008), in which supervised learning updates the preferred directions (PDs) of motor cortical neurons, and reinforcement learning (RL) updates the values of different actions (see Izawa and Shadmerh 2011 for a similar scheme in motor adaptation). In this scenario, the excessive initial value assigned to the compensatory movements following lesion could prevent a smooth transition to normative movements. To validate this hypothesis, we examined whether the model could replicate the "valley of motor recovery", a drop of the performance in the course of transition between the compensatory and normative movements. In rehabilitation of grip task, monkeys with lesions on the motor cortex exhibit a decline of reward probability when shifting from the compensatory grip to the precision grip (Murata et al. 2008). Assuming vector coding of finger movements, the lesion was modeled by the loss of 50% of cells related to thumb flexion and inaccuracy of the compensatory movement was modeled with a larger motor variability. At the initial stage of the training, the success rate gradually increased as RL assigned higher value on the compensatory movements because the precision grip generated a large biased error due the lesion. Then, as in Murata et al. (2008), we progressively increased the task demand by gradually decreasing the goal size. Then, because the compensatory movements with higher variability led to difficulty in satisfying the required accuracy, the RL decreased the value of the compensatory movements. Since PDs of thumb movement have not yet recovered, the success rate decreased. However, after a selecting two movements with roughly equal probability, the PDs recovered, leading to increased reward probability, and in turn to higher value to the precision grip, overcoming the valley. Our simulation results thus suggest that manipulating rewards to guide the patients to use the damaged skill might be effective to overcome the valley of the recovery.

Disclosures: J. Izawa: None. **Y. Murata:** None. **T. Higo:** None. **N. Schweighofer:** None.

Poster

610. Stroke: Impairments and Recovery

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 610.12/P17

Topic: D.17. Voluntary Movements

Support: NIH Grant R01HD059783

Title: Hemisphere-specific motor adaptation deficits in the ipsilesional arm of stroke patients

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Abstract: Our previous research has elaborated hemispheric specialization for different aspects of motor control. The hemisphere contralateral to the dominant arm is specialized for mechanisms that can specify smooth and efficient trajectories under consistent environmental conditions, while non-dominant system is specialized for impedance control mechanisms that can stabilize performance under unpredictable conditions. This hypothesis predicts that adaptation to novel dynamics should be learned more readily by the dominant arm, and that this learning should lead to substantial after-effects, reflecting the learned dynamics. In contrast, the non-dominant arm should be able to adapt through impedance mechanisms, but aftereffects should be reduced or inconsistent, since this system did not "learn" dynamics, but rather impeded the applied loads. This prediction was previously tested in healthy adults by our laboratory (Yadav and Sainburg, 2014) and by Schabowski et al. (2007). We now test whether these interlimb differences in learning can be extended to the hemispheres. We have previous detailed hemisphere specific motor deficits in ipsilesional, non-paretic, arm of stroke patients that reflect loss of the contribution of the ipsilateral hemisphere to motor processes. We now test the hypothesis that learning of novel dynamics is disrupted by left (LHD), but not right hemisphere damage (RHD). Stroke survivors performed reaching movements while holding the handle of a robotic device. The robotic device applied a velocity-squared curl field. Our results indicate a limb X hemisphere interaction, such that patients with LHD showed greater deficits in adapting to the field than those with RHD. In addition, movement errors scaled with the extent of damage (Fugl-Meyer score) for the LHD, but not for RHD patients. These results support the hypothesis that the left hemisphere is specialized for predictive control of limb dynamics.

Disclosures: V. Yadav: None. **D.C. Good:** None. **R.L. Sainburg:** None.

Poster

610. Stroke: Impairments and Recovery

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Topic: D.17. Voluntary Movements

Support: NIH K01 HD060886

NIH T32 NS041231

AHA 14GRNT20460001

Title: Comparing disruption of bihemispheric motor sites on a reaching task in mild and severe arm impairment after stroke

Authors: *R. HARRINGTON[1], E. CHAN[2], S. MOHAPATRA[3], C. J. WUTZKE[3], A. K. ROUNDS[4], D. ABRAHAM[3], M. L. HARRIS-LOVE[3];
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Abstract: Stroke affects over 610,000 people in the United States every year (1) and many are left permanently disabled (2). Chronic post-stroke arm impairment is particularly disabling and existing treatments are of limited efficacy. There are sites in each hemisphere that it may be beneficial to "prime" in order to enhance the effects of a subsequently applied rehabilitation treatment (3; 4). One such region is the dorsal premotor cortex (PMd). Previous research demonstrates that PMd has a role in motor control of the ipsilateral arm, direct ipsilateral and contralateral projections to the spinal cord, and the ability to flexibly compensate for asymmetries in function between hemispheres (5; 6). The role of PMd in post-stroke arm impairment, how it may differ from that of other cortical areas and with severity of post-stroke arm impairment is not known (7). The hypothesis are that nlPMd, not lPMd, has a greater role in recovered reaching function in severe more than mild patients and that nlPMd, but not nlM1, has a greater role in recovered reaching function in severe patients. 30 individuals with (n=15) or without (n=15) active wrist and finger movements after post-stroke arm impairment participated in a reaching task. Participants were asked to reach as quickly as possible with the affected arm to one of the targets in response to a visual 'Go' signal. TMS was applied between the 'Go' signal and movement onset. Double-pulse TMS (ISI 25 ms) was delivered to nlM1, nlPMd and lPMd at 120% of the individual's Resting Motor Threshold (RMT) for unaffected biceps. Change in movement time was greater with TMS applied to nlPMd than to lPMD in the severely impaired but not mildly impaired participants. A trend in the data shows an interaction effect between severity and hemisphere. Within only the severe group, change in movement time was greater with TMS applied to nlPMd but not to nlM1. Data suggest that nlPMd has a greater role in recovered arm reaching in severely impaired patients than lPMd and that this effect is not present in mildly impaired patients. Additionally, data show that this is not an effect of the contralesional

hemisphere as a whole, but a site specific effect to nlPMd as shown through comparison with disruption of nlM1. This study evaluates the role of nlPMd in recovery of arm function. The results of this study lay the foundation to explore nlPMd as a potential site for upregulation as an adjuvant to traditional therapy in severe patients after stroke. Identification of sites to enhance rehabilitation outcomes of severe patients are essential as there are no currently validated treatments and long-term disability is costly to both personal quality of life and national health care costs.

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Poster

610. Stroke: Impairments and Recovery

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Topic: D.17. Voluntary Movements

Support: NIH Grant R01 HD068565-01A1

Title: Motor imagery deficits in individuals with post-stroke hemiparesis

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Abstract: Previous research suggests that simulating movement during motor imagery engages the imaginer's own motor system. One test of the validity of this proposal comes from investigating how motor imagery may be disrupted in individuals with motor dysfunction, such as those who have unimanual motor deficits following stroke. To date, results from motor imagery studies in this population have been inconsistent. Several studies suggest that those with motor impairments are subject to different bodily constraints and thus show disrupted performance on motor imagery tasks, which may be related to functional ability. In contrast, other studies have shown that motor imagery is maintained despite abnormal motor function. To examine the effect of motor impairments on motor imagery, we looked at performance of left and right hemiparetic stroke survivors on the Parsons task. In this task, participants were asked to determine if a picture of a rotated hand was a right or a left hand. Reaction time and accuracy were recorded. Results indicated some evidence for an effect of angle of rotation and direction of rotation on accuracy, as is typically seen in performance on the Parsons task. This suggests that participants were engaging in motor imagery for at least a portion of the task. Consistent with

previous research, there was a trend for those with left hemisphere damage to be less accurate than those with right hemisphere damage. Finally, if motor imagery is based on a modeling of one's own body, there should be a relationship seen between motor impairment severity and motor imagery accuracy. However, no correlation between accuracy on the Parsons task and motor impairment (as measured by Fugl-Meyer scores) was found. This would imply that motor imagery is independent of severity of motor impairment. In summary, results from this study indicate that simulation of one's body during motor imagery is not necessarily constrained by one's motor function and execution abilities.

Disclosures: G. Curtis: None. **S. Jax:** None.

Poster

610. Stroke: Impairments and Recovery

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Topic: D.17. Voluntary Movements

Support: NIH Grant K01HD060886

AHA 14GRNT20460001

Title: Inter-trial variability during forward reaching differs with severity in people post stroke

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Abstract: Studies examining reaching post stroke have primarily focused on people with mild to moderate motor impairment. However, those with the greatest need for improved reaching performance remain under studied. Inter-trial variability of reaching may provide information necessary for the development of individualized rehabilitation protocols. The purpose of this study was to examine inter-trial variability during a seated reaching task between people with different levels of arm impairment severity. We hypothesized that inter-trial variability would be greater in people post stroke with severe impairment (Upper Extremity Fugl-Meyer [UEFM] score <30) versus people with mild or moderate (UEFM score >35) motor impairment. Twenty-eight people post stroke (13 mild/moderate, 15 severe arm impairment) completed 20 forward reaching movements with the paretic arm in response to a visual 'Go' cue to targets located at

80% of their maximum voluntary reach distance. Spatial (movement units (reversals in tangential velocity during a reach)) and temporal (response time, movement time, peak velocity, time to peak velocity) variables were collected with motion capture and a marker placed on the paretic wrist. Coefficients of variation were calculated to determine inter-trial variability of each measure in each participant. The mean coefficient of variation was calculated for participants categorized as mild/moderate or severe. An independent t-test was conducted to identify differences between impairment groups. Compared to participants with mild/moderate motor impairment, severely impaired people had greater inter-trial variability of response time (mild/moderate 0.15, severe 0.30; $p=0.002$) and movement time (mild/moderate 0.19, severe 0.41; $p<0.001$). Inter-trial variability of reaction time however, did not differ between impairment groups (mild/moderate 0.29, severe 0.31; $p=0.799$). Movement units (mild/moderate 0.35, severe 0.61; $p=0.018$), peak velocity (mild/moderate 0.10, severe 0.22; $p<0.001$), and time to peak velocity (mild/moderate 0.19, severe 0.54; $p=0.007$) were also more variable in people with severe motor impairment. These results suggest that people post stroke with severe motor impairment have greater inter-trial variability during a forward reach than people with mild/moderate motor impairment. This increased variability may be influenced by reduced control of paretic arm movement due to reduced integrity of the corticospinal tract. Strokes that include the internal capsule, for example, compromise the relay of motor commands to the paretic arm potentially leading to difficulty controlling the movement.

Disclosures: C. Wutzke: None. **R.M. Harrington:** None. **E. Chan:** None. **S. Mohapatra:** None. **M.L. Harris-Love:** None.

Poster

610. Stroke: Impairments and Recovery

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Program#/Poster#: 610.16/P21

Topic: D.17. Voluntary Movements

Support: Virginia G. Piper Charitable Trust

Title: Toward robotic assessment of proprioception in 3d space

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[5]Sch. of Biol. and Hlth. Systems Engineering, Ira A. Fulton Sch. of Engin. Arizona State Univ., Tempe, AZ

Abstract: Proprioception is the sense of body position, movement, force and effort. Loss of proprioception can affect planning and control of limb and body movements, negatively impacting activities of daily living and quality of life. Proprioceptive assessment is typically performed in the clinic by human examiners, who can potentially provide tactile cues to the subject and who are typically unable to precisely reproduce test positions across trials. Assessments employing planar robots can overcome these limitations but constrain movement and arm configuration within a 2d plane. We have developed a novel paradigm which enables reliable testing of arm proprioception along arbitrary paths in 3d space while also allowing for testing of different arm configurations for the same end point path. A 7-DoF anthropomorphic robot arm (LWR4+, KUKA Inc.) is used for the robotic assessment. Participant's arm is coupled through a trough that stabilizes the wrist and forearm allowing for control of arm posture at the elbow and shoulder. Sensitivity to imposed displacements of the endpoint of the arm are evaluated using a "same-different" task, where subjects are asked to identify if a particular endpoint as the "same" or "different" than a previously visited reference position. The proportion of trials where subjects respond "different" when the stimuli are different ("hit rate"), and where they respond "different" when the stimuli are the same, ("false alarm rate"), are used to calculate d', a measure of sensitivity derived from signal detection theory. Percent correct trials are also calculated. Preliminary data from 4 subjects comparing sensitivity to displacements along a single, vertical axis showed that sensitivity was remarkably consistent across subjects, showing little change in slope for differences in endpoint positions from 1-2 cm, and increasing rapidly in slope thereafter. Across subjects performance reached 75% correct (a standard threshold for discrimination) at a difference slightly greater than 3 cm, consistent with previous studies. The results suggest that the paradigm is suitable for assessment of proprioception in 3d space, which may allow for a more complete characterization of proprioceptive function following nervous system damage. Moreover, the ability to assess multiple joint configurations has the potential to provide a deeper understanding of proprioception with respect to different coordinate systems and a clearer.

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Poster

610. Stroke: Impairments and Recovery

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Topic: D.17. Voluntary Movements

Support: NIDRR FIR Grant H133G110245- Ellis

NIH Grant 2R01HD039343-11A1- Dewald

Title: Employing a binary decision tree algorithm to identify the abduction load threshold at which loss of independent joint control arrests reaching motion in stroke

Authors: *M. D. ELLIS, C. J. LIANG, M. E. RICHARDSON, K. R. SIPPLE, D. O. TAFELSKI, J. P. A. DEWALD;
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Abstract: Quantitative measurements with the ACT^{3D} robotic device have been used to evaluate the impact of loss of independent joint control, or abnormal coupling of shoulder abduction with elbow flexion, on reaching function. The haptic device quantifies the deleterious effects of increasing abduction loads up to and beyond the weight of the arm on planar reaching range of motion. Prior work has validated a laboratory-based protocol, reaching work area, however it is time-inefficient and produces several variables. Here we have reduced the original method by employing a binary decision tree algorithm and targeting the threshold where abduction loading and the associated loss of independent joint control minimizes reaching to zero. The newly developed metric results in a single value. The criterion validity was assessed and we hypothesized that the Maximum Reaching Abduction Load, the shoulder abduction load at which reaching is reduced to zero, would have a strong and significant correlation with a gold standard clinical evaluation of arm function. Ten participants (7 men, 3 women) age 48-69 with chronic stroke (4-29 years post-stroke) scored 16-36/66 on the arm motor Fugl-Meyer Assessment and 3-4/7 on the Ranchos Los Amigos Functional Test for the Hemiparetic Upper Extremity. Maximum Reaching Abduction Load was identified using a protocol that began first by finding the maximum isometric abduction strength using the ACT^{3D} robot. Reaching performance was then assessed with the ACT^{3D} robot using shoulder abduction loads standardized to maximum strength employing a binary decision tree algorithm to quickly identify the Maximum Reaching Abduction Load. Correlation analysis was performed for the robotic and clinical measure using a Spearman rank correlation coefficient with a 2-tailed t-test and alpha level of 0.05. There was a strong and significant correlation ($r_s = 0.685$, $p = 0.029$) between Maximum Reaching Abduction Load (absolute force) and the Arm Motor Fugl-Meyer Assessment. Criterion validity was supported. Importantly, the efficiency of the protocol was reduced substantially from prior reports of 1.5 to 3 hours for the original laboratory-based measure of reaching work area. Further research should be conducted using a larger, more diverse sample size to increase generalizability and establish this metric as the gold standard for quantifying loss of independent joint control following stroke.

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Poster

610. Stroke: Impairments and Recovery

Location: Hall A

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Program#/Poster#: 610.18/P23

Topic: D.17. Voluntary Movements

Support: R00 HD073240

Title: Role of stretch and startle reflexes in falls following stroke: insights from treadmill induced balance perturbations

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Abstract: Stroke is the leading cause of disability with falls being a major risk factor for stroke survivors. The lack of understanding of the mechanisms leading to the high prevalence of falls in this population degrades the efficacy of existing rehabilitation interventions. The long-term goal of the present work is to expand our understanding of factors contributing to falls and establish predictors for the identification of fall-prone individuals. Reflexive compensatory movements (e.g. taking a step during a balance disturbance) play a major role in maintenance of balance and recovery during a fall. Stroke survivors are known to exhibit heightened reflexes. We hypothesized that abnormally expressed stretch and startle reflexes contribute to falls. Studies on these reflexes in stroke survivors have been previously reported, but we are first to investigate these involuntary responses in full-body postural perturbations large enough to provoke a fall. To test our hypothesis, sixteen unilateral stroke survivors were recruited. These individuals were exposed to backward perturbations, evoking a forward step. This resulted in 16 falls out of 86 trials. We characterized performance of fallers and non-fallers using EMG and kinematic data. The implication of stretch reflex in falls was evidenced by the presence of abnormal early EMG activity in the reflex time window of 50-110 ms. In addition to having early onset, this activity exhibited significant perturbation level dependency. This translates directly to velocity dependent nature of spastic stretch reflexes commonly present in stroke survivors. Most notably, this activity was increased with falls and in fallers. These observations support our hypothesis and form the basis for future research on abnormal stretch reflex as potential predictor for falls in stroke population. The role of startle reflex in falls was more complex. Startle trials were observed to involve shorter latencies and increased magnitudes of pre-stepping EMG activity in all monitored muscles. Importantly, these changes were shown not to be beneficial for recovery from falling. This was evidenced by the similarly faster and stronger muscle activity present in

falls. Prevalence of startle was observed to be insignificantly higher in the trials resulting in falls and almost equal between fallers (65%) and non-fallers (63%). All these observations suggest that startle cannot be the main mechanism neither impairing compensatory movements nor facilitating them. In conclusion, our results indicate that heightened stretch responses may contribute to falls, but further research is required to understand the role of startle reflex in these responses.

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Poster

610. Stroke: Impairments and Recovery

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Topic: D.17. Voluntary Movements

Support: NIH Grant R01HD039343

AHA 13PRE14690048

Title: Effects of post-stroke extension/adduction coupling in the lower extremity during gait initiation: preliminary results

Authors: *N. SANCHEZ[1], A. C. DRAGUNAS[2], J. P. A. DEWALD[1], K. E. GORDON[1]; [2]Biomed. Engin., [1]Northwestern Univ., Chicago, IL

Abstract: Introduction: Previous research by our group has demonstrated that during hip extension tasks, post-stroke individuals generate spontaneous grouped extension/adduction torques in both legs, referred to as an extensor synergy. Specifically, in isometric conditions, when individuals were instructed to generate a hip extension torque a concurrent abnormal hip adduction torque was observed. This pattern was identified in both the paretic and non-paretic extremity. In the present study, we quantified how these hip joint torque coupling constraints translate to gait initiation, a dynamic task. During gait initiation each limb has a very specific role: the leading leg is in charge of foot placement while the supporting leg generates forward propulsion and lateral stability. In order to accomplish these tasks, the supporting leg simultaneously generates hip extension and abductions torques. Given the known extensor synergy, we propose to assess how individuals post-stroke accomplish a dynamic task requiring simultaneous generation of hip extension and abduction torques. We hypothesize that the extension/adduction constraint at the hip observed isometrically will affect gait initiation given

the inability to combine hip extension with hip abduction. Methods: Two chronic stroke individuals and two age-matched controls performed a gait initiation task. A motion capture system and force plates recorded kinematics and kinetics. With the aid of visual feedback, subjects began each trial with their body weight equally distrusted between their two limbs. When the weight distribution was held stable for three seconds, a "GO" cue appeared on the screen. Individuals initiated gait leading with either the paretic or non-paretic extremity five times. The leading leg was determined randomly before each trial. Data was processed and used to calculate internal moments about the hip joint. Results: Post-stroke individuals generated a hip adduction torque offset before gait initiation on both extremities. As soon as an extensor moment was generated, this adduction moment increased as a function of hip extension; no net hip abduction torque was generated. In contrast, control individuals began the trial with a slight hip abduction moment. Once hip extension was generated on the support leg, no changes in hip abduction torque were observed, indicating that hip abduction and hip extension moments were controlled independently. Implication: The abnormal joint torque coupling pattern observed during gait initiation may help explain the underlying mechanisms for increased pelvic instability in the transverse plane reducing balance in post-stroke individuals.

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Poster

610. Stroke: Impairments and Recovery

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Topic: D.17. Voluntary Movements

Support: NICHD-NCMRR K01 Grant HD060693

Title: Reduced pedaling-related brain activation volume post-stroke does not depend on task performance

Authors: *B. CLELAND, S. SCHINDLER-IVENS;
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Abstract: Numerous studies have shown that movement-related brain activation, as measured with functional imaging, is altered after stroke. These observations are suggestive of injury-related and/or recovery-related neuroplasticity. However, stroke is also associated with altered task performance, which confounds the interpretation of imaging data. Our laboratory recently

encountered an example of this performance confound when we discovered that pedaling-related brain activation volume during fMRI was reduced in stroke survivors as compared to controls. Reduced volume could be due to neuroplasticity, or it could be the result of altered pedaling performance. Here, we examined this issue by using passive pedaling to minimize between-group differences in performance. We hypothesized that, if reduced volume of brain activation post-stroke was due to altered pedaling performance, then between-group differences would be reduced or eliminated during passive pedaling. Stroke (n=6, 66 ± 8 yrs) and control subjects (n=5, 61 ± 4 yrs) performed passive and volitional pedaling during fMRI. During passive pedaling, subjects relaxed their limbs while an investigator moved the pedals. Volitional pedaling was performed with no investigator intervention. We used a block design consisting of 3 runs each of passive and volitional pedaling at 2 workloads. Each run consisted of 20 sec of pedaling followed by 20 sec of rest, repeated 5 times. To identify significantly active voxels, general linear modeling was used to fit blood-oxygenation-level-dependent (BOLD) signals to a canonical function. A family-wise error rate of $p<0.05$ was achieved through Monte Carlo simulation. Volume of activation was extracted from active regions in the sensorimotor cortex, namely primary motor cortex (M1), primary sensory cortex (S1), and Brodmann's area 6. Results show that, regardless of condition (passive, volitional), brain activation volume was lower in stroke subjects as compared to controls ($F=4.96$, $p=0.053$). Mean ± SD values for passive and volitional pedaling were 12959 ± 9650 μL, 10791 ± 5994 μL (load 1), and 10378 ± 10800 μL (load 2) in the stroke group and 20633 ± 11333 μL, 23591 ± 8518 μL (load 1), and 23355 ± 7792 μL (load 2) in controls. There was no main effect of condition ($F=0.027$, $p=0.973$) and no group*condition interaction ($F=0.835$, $p=0.469$). Our observations suggest that reduced pedaling-related brain activation volume post-stroke does not depend on task performance, as reduced volume was apparent during passive pedaling when performance differences were minimized. Hence, other explanations for reduced volume, including neuroplasticity, should be considered.

Disclosures: **B. Cleland:** None. **S. Schindler-Ivens:** None.

Poster

610. Stroke: Impairments and Recovery

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Topic: D.17. Voluntary Movements

Support: CIHR 2012-2017

Title: Grey and white matter changes associated with periodic leg movement during sleep: a magnetic resonance imaging study

Authors: ***M.-A. D. GAREAU**, A.-A. BARIL, D. GILBERT, N. GOSSELIN, A. DESAUTELS;
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Abstract: INTRODUCTION: Periodic leg movements during sleep (PLMS) are repeated and stereotyped motor activity characterized by extension of the hallux and dorsiflexion of the ankle, with occasional flexion of the knee and hip. Recent studies showed a temporal association between PLMS and activation of the sympathetic nervous system, characterized by an important increase in blood pressure and heart rate. Chronic high blood pressure may impair the cerebral microvasculature and compromise the cerebral white matter (WM) integrity, which could also lead to grey matter (GM) damage. In this study, we investigated the presence of WM and GM changes using magnetic resonance imaging (MRI) in subjects presenting PLMS. METHODS: MRI sequences (T1-weighted Multi-Echo MPRAGE; Diffusion tensor imaging (DTI) with 64 directions) were acquired for 26 subjects (6 Females; 64.0 ± 6.6 years old) presenting varying levels of PLMS severity (PLMS index: 20.8 ± 22.5 events/h, range: 0.0 to 79.3 events/h). GM density was measured using voxel-based morphometry and DTI was used as a correlate of the WM integrity using track-based spatial statistics. Maps of DTI metrics were calculated for each subject and included fractional anisotropy, mean diffusivity, axial diffusivity and radial diffusivity. Correlational analyzes were performed between PLMS characteristics (index, association with arousal, duration, inter-movement interval) and neuroimaging variables with a height threshold of $p<0.001$ uncorrected for multiple comparisons and an extended threshold of 50 contiguous voxels. RESULTS: No correlation was found between DTI metrics and PLMS characteristics. However, a higher PLMS index was correlated with reduced GM density in three regions, namely the right supramarginal gyrus, the right mid-cingulate area and the left middle temporal gyrus. longer inter-movement intervals were associated with reduced GM density in a large cluster extending from the left cerebellum to the left lingual gyrus. Finally, a longer duration of PLMS was associated with reduced GM density in the left cerebellum and the left inferior parietal lobule. CONCLUSIONS: PLMS characteristics that reflected higher severity, i.e. higher index, longer PLMS duration and longer inter-movement interval, were associated with reductions in GM density in the parieto-temporal areas, the cerebellum and the cingulate gyrus. However, no changes were found in WM integrity. Although the pathophysiological substrate and clinical significance of these findings are unclear and results need replication, the association observed in our cohort suggests that PLMS may alter brain structure.

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Poster

610. Stroke: Impairments and Recovery

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Topic: D.17. Voluntary Movements

Support: NIH Grant HD053727

Title: Neuromuscular control bandwidth at the elbow following stroke

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Abstract: Motor deficits after stroke may reflect changes in the timing of muscle initiation and termination, which can degrade joint torque production and impede motor coordination. Better understanding of these deficits may guide development of rehabilitative strategies to restore functional movement post-stroke. Here, we quantified deficits of control bandwidth in 4 hemiparetic stroke survivors (HS) and 4 age-range matched, neurologically intact controls (NI) during 2 isometric torque-tracking tasks. The affected (HS) or preferred (NI) arm was positioned horizontally with the elbow flexed to 90° and the forearm attached to a custom handle that measured elbow joint torque. Surface electromyograms (EMG) were recorded from elbow flexors and extensors. Maximal voluntary contractions (MVCs) were collected for elbow flexion and extension. Subjects viewed a computer screen that cued either an oscillating 'chirp' torque-tracking target (oscillation frequency increased linearly from 0.1 to 20 Hz within each 120 s trial) or discrete, step changes in desired elbow torque, transitioning pseudorandomly between flexion and rest or extension and rest. Real-time feedback of torque at the elbow was also provided. Torque target magnitude was defined as 20% of that measured during MVC. EMGs were zero-meaned and notch filtered (60 Hz), rectified, low-pass filtered (20 Hz) and normalized to MVC. Muscle pairs were used to calculate 2 measures of joint coordination at the elbow: agonist / antagonist co-activation (CoA) and reciprocal activation (ReA). Control bandwidth was defined as the tracking frequency for which torque-tracking amplitude dropped below 71% of baseline performance. HS demonstrated reduced torque-tracking bandwidth relative to NI controls (0.34±0.02 Hz vs. 1.28±0.58 Hz, respectively). This performance deficit was coincident with a two- to three-fold increase in flexor / extensor CoA at failure, but no consistent group-wise

change in ReA. In step tracking, reaction times were greater post-stroke (HS: 361±125 ms; NI: 161±70 ms) as were torque development times (HS: 697±163 ms; NI: 405±88 ms) and torque relaxation times (HS: 651±112 ms; NI: 415±85 ms). Surprisingly, we did not find a consistent inability to produce coordinated reciprocal activations during the step transitions post-stroke. Instead, performance deficits appeared to be related to increased flexor / extensor CoA. A computational model of performance in the chirp-tracking task suggests that neuromuscular control bandwidth is limited by deficits in the temporal activation and deactivation of individual muscles, thus contributing to deficits in muscular coordination.

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Poster

610. Stroke: Impairments and Recovery

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 610.23/P28

Topic: D.17. Voluntary Movements

Support: NIH R01 NS053606

Title: A model identifiability analysis for separating the relative neural and muscular contributions to weakness after stroke

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Abstract: Weakness is the most common motor deficit following stroke, yet current diagnostic tools do not elucidate its underlying neuromuscular impairments. Researchers have attempted to diagnose these impairments by comparing biomechanical models to experimental data. However, experimental data tend to be sparse and noisy, while there are often many model parameters to be estimated. Since experiments in human motor control are often time consuming and laborious, there is a need for a single test that provides sufficient information to unambiguously estimate all of the free model parameters. Using a simplified biomechanical model of the human elbow dynamics, we tested whether kinematic data contains sufficient information to recover a known combination of muscle atrophy and decreased motor commands. Our model consisted of a single arm segment corresponding to the forearm, restricted to move in the horizontal plane by rotating about a hinge joint representing the elbow. The joint was actuated by one antagonistic muscle pair consisting of the biceps and triceps, each described by a Hill-type muscle model. The free

model parameters were: 1) the optimal biceps force (F_(opt,biceps)=800[N]), 2) the optimal triceps force (F_(opt,triceps)=600[N]), and 3) a proportional decrease in motor commands (α=0.75). We fitted these three model parameters 100 times, minimizing the residual error between the model predictions and the simulated output kinematics. For each model regression, the optimization algorithm was initialized with a different randomized population. This resulted in 100 sets of fitted model parameter values. We found that these calibrated parameters were functionally related to each other, meaning that there are an infinite number of parameterizations that explain the simulated kinematics equally well. Further analysis showed that including EMG measurements allowed us to unambiguously recover the true, unique solution. In future work we will build on these initial results by analyzing more complex human arm models and fitting them to experimental data obtained from both neurologically intact individuals and stroke survivors.

Disclosures: P. Cooman: None. **F. Huang:** None. **J.L. Patton:** None.

Poster

610. Stroke: Impairments and Recovery

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 610.24/P29

Topic: D.17. Voluntary Movements

Support: Foundation for Physical Therapy

California Physical Therapy Fund

Title: Relationship between skilled reach performance and corpus callosum integrity in individuals with mild motor impairment after stroke

Authors: *J. C. STEWART[1], M. O'DONNELL[1], K. HANDLERY[1], C. J. WINSTEIN[2]; [1]Univ. of South Carolina, Columbia, SC; [2]USC, Los Angeles, CA

Abstract: Changes in white matter pathways can occur after stroke due to both direct and remote effects of the lesion that correlate with motor impairment. While deficits in skilled reaching after stroke have been well documented, the relationship between white matter structural integrity and measures of skilled reach performance are not currently known. The purpose of the current study was to examine the correlation between reach kinematics and the integrity of two white matter pathways: the corticospinal tract and the corpus callosum. Eleven individuals with mild motor impairment due to stroke (mean UE FM motor score 54.2±7.6; months post-stroke 62.5±42.4) and no lesion in the cerebral peduncle or the corpus callosum reached to targets displayed in two

directions (ipsilateral, contralateral). Mean movement time, peak velocity, peak acceleration, and endpoint error were extracted for reaches with both the paretic and nonparetic arms. Fractional anisotropy (FA) was calculated from diffusion tensor images and used to determine structural integrity of the corticospinal tract in the cerebral peduncle and the motor and premotor sections of the corpus callosum. Reaches with the paretic arm had significantly lower peak velocity, lower peak acceleration, longer movement times and greater endpoint error than reaches with the nonparetic arm ($p<0.02$). The premotor section of the corpus callosum showed a significant correlation with movement time ($r=-0.64$) and peak acceleration ($r=0.61$) for reaches with the paretic arm and movement time ($r=-0.75$) and peak acceleration ($r=0.77$) for reaches with the nonparetic arm. No measures of reach performance correlated with FA in the motor section of the corpus callosum or the corticospinal tract. Additionally, there was no correlation between UE FM motor score and SIS hand domain score and FA in any of these brain regions. The structural connections between the two premotor cortices, areas commonly reported to support motor recovery after stroke, may play an important role in the control of skilled reach behavior in individuals with mild motor impairment. These results may have implications for interventions that target skilled reaching or include brain stimulation in combination with functional task training.

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Poster

610. Stroke: Impairments and Recovery

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 610.25/P30

Topic: D.17. Voluntary Movements

Support: NIDRR grant H133G120287

Title: Improvement of voluntary control of post-stroke paretic hands using a novel assistive system - Rein Hand: preliminary findings

Authors: *J. YAO[1], C. CARAMONA[1], J. SULLIVAN[1], K. WILKINS[1], E. LEE[1], A. MOORE[1], N. PARMANN[1], S. WOJTON[1], Z. GARCIA[2], J. P. A. DEWALD[1];
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Abstract: Purpose: Approximately, 75% of survivors with moderate to severe stroke (i.e., our target population) lose hand function. Neuromuscular electrical stimulation (NMES) has been shown to be successful in improving wrist muscle strength and reducing muscle tone. Unfortunately, no methods to date have proven to be effective in improving voluntary functional hand control in our target population, partially because the previous NMES in not employed in a functional context requiring changes in shoulder abduction loading and reaching and retrieval activities. In order to address this gap in functionality, this study tests a newly developed electromyography-triggered NMES system - ReIn-Hand - to regain voluntary hand opening in this population during functional activities. We hypothesize that using the ReIn-Hand system during functional activities will help our target population to improve voluntary hand opening function. Methods: Two individuals with moderate to severe chronic stroke completed a total of 15-22 sessions, 3 sessions per week. In each training session, subjects used the paretic arm to perform 20-30 trials of tasks involving reaching, grasping, and releasing with the assistance of ReIn-Hand and various levels of shoulder abduction loading. Active range of motion, Chedoke MacMaster (CMcM) (stroke-assessment hand portion), Semmes-Weinstein monofilament test, the Nottingham Assessment (stereognosis portion), and grip strength were assessed before and after the intervention. Additionally, S2 was assessed with the box and block test (BB). Results: Pre-intervention, both subjects demonstrated decreased voluntary hand control, and the expression of shoulder abduction with elbow/wrist and finger flexion. Additionally, Subject 1 (S1) had sensory impairment and increased muscle tone, while subject 2 (S2) had muscle weakness, mild sensory impairment, and mild increase in muscle tone. By the end of the intervention, both subjects had improved sensation, grip strength and increased voluntary index finger extension at the metacarpal-phalangeal joint. S2 demonstrated improvements in CMcM, and increased gross manual dexterity (BB from 0 to 3-6 blocks during the last week of intervention). Conclusions: These preliminary results suggest that using the ReIn-Hand during functional reach/grasp activities is effective in improving voluntary hand control and sensory perception in individuals with moderate to severe chronic stroke. Further investigation is needed to evaluate the effectiveness of the ReIn-Hand system in larger populations and using additional quantitative measurements.

Disclosures: **J. Yao:** None. **C. Caramona:** None. **J. Sullivan:** None. **K. Wilkins:** None. **E. Lee:** None. **A. Moore:** None. **N. Parmann:** None. **S. Wojton:** None. **Z. Garcia:** None. **J.P.A. Dewald:** None.

Poster

610. Stroke: Impairments and Recovery

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 610.26/P31

Topic: D.17. Voluntary Movements

Support: National Stroke Foundation of Australia Small Project Grant

The Centre for Advanced Imaging, University of Queensland

Title: Feasibility of transcranial Random Noise Stimulation combined with repetitive reaching practice in stroke survivors with chronic and severe paresis: A triple blind pilot RCT

Authors: *K. S. HAYWARD[1,2,4], K. L. RUDDY[5], D. LLOYD[3], S. G. BRAUER[2], R. N. BARKER[4,6], R. G. CARSON[7,8];
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Abstract: Background: Reaching training can promote functional recovery in stroke survivors with severe arm paresis. To amplify cortical activity and enhance functional benefits, non-invasive brain stimulation (eg transcranial-direct current stimulation) has been combined with training, but with limited success in people with severe paresis. An alternative approach is transcranial random noise stimulation (tRNS). Here, it is thought that by adding random noise, the detection of weak stimuli (or the information content of a signal) will be enhanced and thus, boost the adaptive potential of the stimulated cortical area. Aim: Investigate the feasibility of combining reaching training with tRNS timed to coincide with the generation of a voluntary motor command in stroke survivors with chronic and severe arm paresis. Methods: A triple-blind pilot RCT was completed. Four stroke survivors were randomly allocated to 4-weeks of reaching training with active (n = 2) or sham (n = 2) tRNS delivered over C3/C4. tRNS delivery was triggered by a 'go' signal so as to coincide stimulation with a voluntary movement attempt and ceased after 5-seconds. At this point, electrical stimulation to triceps brachii could be triggered to enable full range reaching. To determine feasibility we considered 1) ability to complete repetitive training, 2) improvement in clinical outcomes between time-points (pre-, post-training, follow-up) and 3) adverse events. To determine if ability to engage in training was contingent upon structural integrity of descending white matter projections, diffusion weighted imaging of the posterior limb of the internal capsule (PLIC) was undertaken. The asymmetry index (AI) between lesioned and non-lesioned hemisphere PLIC projections was calculated, with an AI >0.15 classified as loss beyond the point of no return (PNR). Results: All participants completed all training sessions, engaged in repetitive practice and demonstrated some clinical improvements, irrespective of tRNS group and PNR classification (Table 1). There were no

adverse events. Conclusion: Reaching training that includes tRNS timed to coincide with the generation of voluntary motor commands is feasible. Table 1: Characteristics & outcomes.

ID	AI	tRNS group	Total repetitions	Triceps strength (/15)			Motor Assessment Scale: 6 (/6)			REACH (score /5)		
				Pre	Post	FU	Pre	Post	FU	Pre	Post	FU
P1	0.02, PNR	Active	1763	10	12	12	1	1	1	1	2	2
P2	0.11, PNR	Sham	1128	3	6	7	2	3	2	0	1	1
P3	1*, >PNR	Active	1015	3	3	2	0	1	1	0	0	1
P4	1*, >PNR	Sham	1696	3	6	6	1	1	1	0	0	1

*No extractable PLIC projections.

Disclosures: **K.S. Hayward:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SMART Arm Pty Ltd.. **K.L. Ruddy:** None. **D. Lloyd:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SMART Arm Pty Ltd. **S.G. Brauer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SMART Arm Pty Ltd. **R.N. Barker:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SMART Arm Pty Ltd. **R.G. Carson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SMART Arm Pty Ltd..

Poster

610. Stroke: Impairments and Recovery

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 610.27/P32

Topic: D.17. Voluntary Movements

Support: NIH R01 HD044295

Title: Mobility rehabilitation in acute stroke using a wearable ankle robot

Authors: *D. JIN[1], Y. REN[1], K. CHEN[1], R. HARVEY[1], E. ROTH[1], S. PRABHAKARAN[2], L.-Q. ZHANG[1];
[1]Rehabil. Inst. of Chicago, Chicago, IL; [2]Inst. for Publ. Hlth. and Med. (IPHAM),Northwestern Univ. Clin. and Translational Sci. Inst. (NUCATS), Chicago, IL

Abstract: Background and Purpose: Over 7 million individuals currently in the US with stroke-related disabilities, joint impairments of paretic limb is a prevalent symptom and closely associated with limitation in ambulation post stroke. In acute stroke, 50-70% of stroke survivors regained functional independence, it was reported that the first few months post stroke is critical in neuroplasticity and motor recovery. Presently, effective treatment options for ankle impairment and mobility are limited; there is a lack of devices and protocols for in-bed acute stroke rehabilitation. In treating with joint impairments post stroke, stretching has been commonly used to reduce joint stiffness and increase range of motion. However, there is a lack of convenient and effective ways in regular treatment to conduct controlled passive stretching and motivating active movement training with quantitative outcome evaluation. In this study, in-bed wearable robot training involving stretching and active movement training was investigated. Methods: Fifteen patients with acute stroke participated in the combined passive stretching and active movement training using a wearable robot in an in-patient setting (45 minutes/session, 3~5×/week, total 18 sessions). They continued receiving standard of care during the study. One way repeated measures ANOVA with repeated measures was used to compare clinical and biomechanical outcome measures. Results: Results showed improvements after the multiple sessions of training with Fugl-Meyer Lower Extremity (LE) increased from 16.0 ±8.4 to 18.6 ± 7.1 ($p<0.01$), STREAM total score from 50.0±31.2 to 59.7±30.6 ($p<0.05$), Berg Balance Score from 23.0±19.5 to 28.7±20.1 ($p<0.05$). The ankle modified Ashworth Scale decreased from 2.8±0.8 to 2.0±0.9 ($p=0.05$). Ankle dorsiflexion active range of motion increased from -0.9±7.4 to 4.1 ± 7.6°(- means it was still in plantar flexion, $p=0.004$). Dorsiflexor strength increased from 1.8±5.6 Nm to 4.4±8.1 Nm ($p=0.05$). Plantar flexor strength increased from 9.1±12.7 to 13.1±13.2 Nm ($p<0.05$). Conclusions: Robot-aided acute stroke rehabilitation demonstrated improvements in terms of biomechanical and clinical outcomes. The results supported clinical use of this novel device coupled with clinical therapy to promote sensorimotor outcomes for the acute stroke survivors. Limitations of this study include small sample and lack of a control group.

Disclosures: **D. Jin:** None. **Y. Ren:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rehabtek LLC. **K. Chen:** None. **R. Harvey:** None. **E. Roth:** None. **S. Prabhakaran:** None. **L. Zhang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rehabtek LLC.

Poster

610. Stroke: Impairments and Recovery

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 610.28/P33

Topic: D.17. Voluntary Movements

Support: NIH Grant NS084069

Title: Designing myoelectric computer interfaces to improve arm function in chronic stroke

Authors: *M. W. SLUTZKY, E. M. MUGLER, E. W. LINDBERG;
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Abstract: Stroke causes the most disability of any disease. In addition to weakness and impaired sensation, a stroke can also affect arm function by impairing muscle activation patterns. This abnormal co-activation can prevent subjects from fully participating in standard physiotherapy. We have designed a myoelectric-computer interface (MCI) paradigm that maps activations of a pair of abnormally coupled muscles to orthogonal components of computer cursor movement (Wright et al., Neurorehabilitation and Neural Repair 2014). Stroke subjects learn to decouple these muscle activations by moving the cursor to targets along the mapping directions in a computer game. In this study, we are investigating which aspects of MCI design contribute most to arm function improvement. Chronic stroke survivors use the MCI to decouple 3 muscle pairs in the upper arm over 18 sessions. We are evaluating the effects of duration of training (either 60 or 90 minutes per session) and isometric vs. movement-based muscle activations to control the MCI. We have also improved game design and level of difficulty to enhance motivation. We measure the following outcome metrics at weeks -2, 0, 2, 6, and 10 relative to the start of training: level of co-activation and arm joint kinematics during free reaching, Fugl-Meyer Assessment (FMA), Wolf Motor Function Test (WMFT), Motor Activity Log (MAL), and Modified Ashworth Scale (MAS). Our early results, in 4 subjects, demonstrated improvement from baseline to the end of training. Co-activation levels declined in all subjects in the targeted muscles, and elbow extension improved substantially in all subjects. Less-sensitive functional and impairment scores showed modest improvement (FMA +2.1, Wolf -25.6 s, MAL +12.5), and spasticity decreased by 5.8 points. We expect further testing will reveal more detailed effects of dose and movement-based training on functional outcomes. These results suggest that MCI training can reduce abnormal co-activation and spasticity and improve upper arm function in chronic stroke survivors. If successful, this paradigm could have a broad impact, since it could be made into an inexpensive and portable device that many survivors could incorporate into their daily routine.

Disclosures: **M.W. Slutzky:** None. **E.M. Mugler:** None. **E.W. Lindberg:** None.

Poster

610. Stroke: Impairments and Recovery

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 610.29/P34

Topic: D.17. Voluntary Movements

Support: Canadian Partnership for Stroke Recovery

Title: Testing the feasibility of way-finding combined with aerobic activity after stroke

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Abstract: Stroke is one of the leading causes of long term disability in North American adults, leading to deficits in motor function, cardiovascular capacity and cognitive impairments. Exercise interventions have demonstrated positive impacts on brain health in various populations, and therefore may aid in the rehabilitation of cognitive, sensorimotor and cardiovascular impairments in a stroke population. However, current protocols challenge physical capacity but do not concurrently challenge executive function. We propose that stroke patients are capable of more fully engaging in executive tasks while performing aerobic activity. Specifically, we challenged executive function by having participant's way-find through the rendered version of street view within Google Earth™. Way-finding was chosen because it is a complex cognitive task, and is considered an ecologically valid task with natural links to locomotion. The objective of this study was to determine the feasibility of combining aerobic activity and way-finding in a stroke population, to examine if there were group differences in dual task performance. Four stroke patients and 3 healthy adults performed aerobic activity on a semi-recumbent stepper. Participants completed 4 five minute blocks of aerobic activity with approximately 2 minutes between blocks. Participants were asked to step at a self-selected cadence. Tasks alternated between activity alone and activity coupled with way-finding. Cadence, heart rate (HR), and rate of perceived exertion (RPE) were recorded as well as geographic coordinate data from Google Earth™ in order to determine performance of the way-finding task. Stroke patients displayed the same behavioral characteristics as control subjects in

both conditions. Both groups showed decreases in cadence when executive function was simultaneously challenged with way-finding. All participants were able to maintain or increase target power output and HR throughout activity. This sample of stroke patients demonstrated the capacity to couple aerobic activity with the executive task of way-finding without sacrificing workload. Ongoing work is implementing this protocol as a training program in a stroke population. Funding support: Canadian Partnership for Stroke Recovery

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Poster

611. Brain Machine Interface: Methods and Technology

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 611.01/P35

Topic: D.18. Brain-Machine Interface

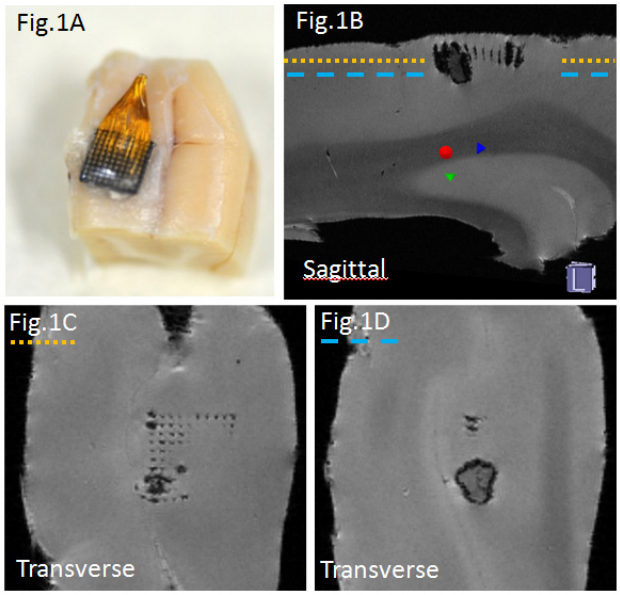
Support: ARC Special Research Initiative 'Bionic Vision Australia'

Title: Assessment of tissue using high resolution MRI following intracortical multi-shank microelectrode array implantation

Authors: *A. J. WOOLLEY[1,3], A. BONGERS[2], N. H. LOVELL[1], J. W. MORLEY[3]; [1]Grad. Sch. of Biomed. Engin., [2]Biol. Resource Imaging Laboratory, Mark Wainwright Analytical Ctr., Univ. of New South Wales, Sydney, Australia; [3]Sch. of Med., Univ. of Western Sydney, Sydney, Australia

Abstract: Brain penetrating, multi-shank microelectrode arrays, like the 'Utah Array' (Blackrock Microsystems), are invaluable tools for neurophysiologists. They are also potentially ground-breaking medical devices, holding great promise as neuroprosthetic implants. However the acute and long-term tissue impact of these devices on surrounding cerebral cortex is difficult to fully characterize using the histological methods that are typically employed. Work presented here describes results from utilizing a high resolution MRI system (9.4 Tesla) to assess brain tissue following implantation of intracortical, 100-shank electrode arrays. Imaging was performed on blocks of fixed feline brain tissue (Fig.1A). Areas of sub-surface hemorrhaging were visible in the MRI data in tissue collected 2-days following surgery (Fig.1B,1C,1D). These hemorrhages and micro-hemorrhages were not visible at all depths in the tissue, and could be found in cortical layers below the implant shanks, an area easily overlooked by investigators using typical histological analysis methods. Electrode tracks were clearly visible within tissue in

which the device was explanted, provided a reasonable guide to the depth of device implantation upon tissue collection and fixation. MRI data collected with arrays *in situ* demonstrates that similar methods may be employed at the termination of future, long-term studies to potentially document dural encapsulation and retraction of devices from brain tissue. Overall, high resolution MRI is demonstrated to be a promising method to assess important 'wide view' features of the tissue response to implanted microelectrode arrays, and may be utilized to fill an important gap in our understanding of how multi-shank implants impact surrounding brain tissue.



Disclosures: **A.J. Woolley:** None. **A. Bongers:** None. **N.H. Lovell:** None. **J.W. Morley:** None.

Poster

611. Brain Machine Interface: Methods and Technology

Location: Hall A

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Program#/Poster#: 611.02/P36

Topic: D.18. Brain-Machine Interface

Support: DARPA RCI N66001-12-C-4025

University of Wisconsin-Madison Graduate School

University of Wisconsin-Madison Alumni Association

Title: Intrinsic imaging of the wounding response around implanted neural devices

Authors: *C. R. ESQUIBEL[1], S. K. BRODNICK[1], J. P. NESS[1], J. R. NOVELLO[1], A. A. SCHENDEL[1], H. C. LEE[4], K. J. OTTO[5], L. A. KRUGNER-HIGBY[2], S. O. POORE[3], K. W. ELICEIRI[1], J. C. WILLIAMS[1];
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Abstract: Although fibrillar collagen is not commonly found in the brain parenchyma, complex networks of fibrillar collagen can be observed around neural devices, including but not limited to implanted electrodes. Previous studies in the central nervous system have implicated microglial and astrocytic mediated responses to device implantation as primary factors in implant failure. The role of the extracellular matrix (ECM) that encompasses these cells however, is not well understood. Collagen deposition and remodeling throughout the ECM in tumor models has shown a potentiation of invasive cancer cells migrating along collagen fibers. It would therefore follow that the collagen fibers that form within a wound site could provide the pathway necessary for the reactive immune response observed following neural device implantation, and may be critical to understanding the biological mechanisms underlying device failure. It may also have implications for the logical design of devices for longer lasting brain-machine interfaces. This study used second harmonic generation (SHG) imaging on a multiphoton microscope to observe the extent to which fibrillar collagen is involved in the ECM of neural wounds. SHG imaging is attractive to neuroscientists not only because the number and orientation of detectible collagen fibers can be quantified, but also because the imaging takes advantage of an intrinsic property of collagen fibers without the addition of extrinsic dyes or fluorophores. Thus, SHG imaging has great potential for further neurosurgical applications.

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Poster

611. Brain Machine Interface: Methods and Technology

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Topic: D.18. Brain-Machine Interface

Support: University of Wisconsin-Madison Graduate School

University of Wisconsin-Madison Alumni Association

NRF 2013R1A1A20655030

Title: Transparent graphene micro-electrocorticography and its electrochemical impedance spectroscopy

Authors: *D.-W. PARK[1], S. K. BRODNICK[2], D.-H. BAEK[2], A. SCHENDEL[2], S. MIKAEL[1], T. RICHNER[2], J. NESS[2], F. ATRY[3], J. NOVELLO[2], H. KIM[1], S. THONGPANG[4], R. PASHAIE[3], Z. MA[1], J. WILLIAMS[2];
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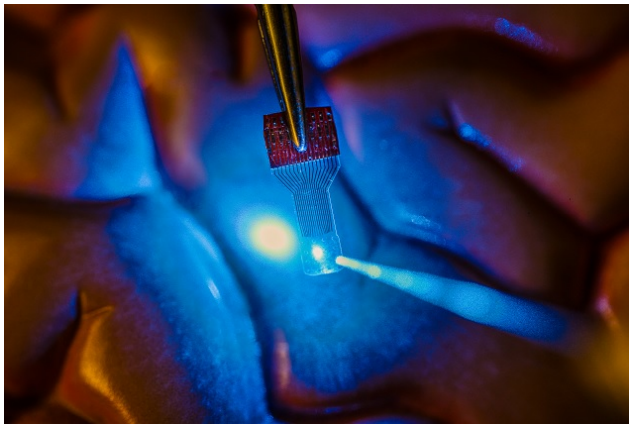
Abstract: The transparent, graphene-based micro-electrocorticography (μ-ECoG) electrode array is an implantable device that is capable of advanced *in vivo* neural imaging, electrophysiological recordings, and optogenetic stimulation. Previous *in vivo* studies with conventional metal electrode were limited to monitoring the tissue surrounding μ-ECoG electrode sites due to the opaqueness of the metal. Optical stimuli through the electrode sites and traces were also impossible with metal electrode arrays. Graphene, a novel material made of carbon atoms, has broad wavelength transparency from ultraviolet (UV) to infrared (IR). In addition, electrical conductivity, mechanical flexibility, and biocompatibility of graphene make it a promising material for the next-generation neural electrode. The transparent graphene μ-ECoG array placed under a cranial window implanted over the cerebral cortex in rodents allows for chronic investigations of the underlying neural tissue while simultaneously performing electrophysiology and optogenetic experiments. In this work, *in vivo* imaging of the cortical vasculature through the transparent electrode sites has been shown via fluorescence microscopy and 3D optical coherence tomography. Optogenetic activation of focal cortical areas directly beneath electrode sites has been demonstrated in transgenic Thy1::ChR2 mice. The graphene remains electrically viable for chronic recording for extended time periods (months). For the fundamental understanding of the graphene μ-ECoG, electrochemical impedance spectroscopy (EIS) has been performed and an equivalent circuit has been modeled. The result shows that the graphene device is capacitive at lower (<10 Hz) or higher (>1000 Hz) frequency, and rather faradaic near 100 Hz. This study demonstrates an array of interfacing abilities of the graphene μ-ECoG and its utility for neural applications.



Disclosures: **D. Park:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Wisconsin Alumni Research Foundation. **S.K. Brodnick:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison. **D. Baek:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison. **A. Schendel:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison. **S. Mikael:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison. **T. Richner:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison. **J. Ness:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison. **F. Atry:** A. Employment/Salary (full or part-time):; University of Wisconsin-Milwaukee. **J. Novello:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison. **H. Kim:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison. **S. Thongpang:** A. Employment/Salary (full or part-time):; Mahidol University. **R. Pashaie:** A. Employment/Salary (full or part-time):; University of Wisconsin-Milwaukee. **Z. Ma:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison. **J. Williams:** A. Employment/Salary (full or part-time):; University of Wisconsin-Madison.

Poster

611. Brain Machine Interface: Methods and Technology

Location: Hall A

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Program#/Poster#: 611.04/P38

Topic: D.18. Brain-Machine Interface

Support: NRF Grant No.2013R1A1A20655030

Title: A mesh structure based polyimide microelectrode for long-term epidural-ECoG recording

Authors: *D.-H. BAEK[1,3], S. K. BRODNICK[1], D.-W. PARK[2], H. KIM[2], S.-H. LEE[3], J. C. WILLIAMS[1];
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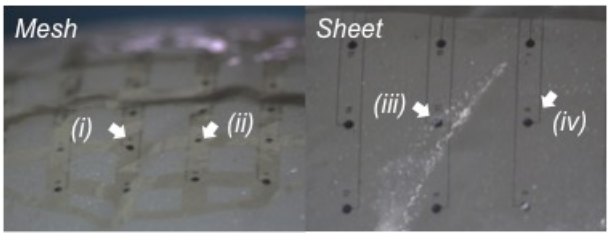
Abstract: Epidural electrocorticography (ECoG) activity may be more reliable and stable than single-unit recordings such as are found with intracortical implantable devices. These devices are limited by mechanical mismatching and cellular reactive responses due to differences in the elastic modulus and immune response. Consequently, we evaluated the feasibility of long-term recording of epidural ECoG activity by developing flexible and mesh structured polyimide (PI) based multi-electrode arrays. We designed a multi-channel electrode array with a mesh structure for more conformal contact with a curved surface such as the surface of the cortex. We compared the contact capability of mesh PI electrodes with conventionally used sheet PI electrodes. The electrical properties of the mesh PI electrode were evaluated for 4 weeks *in vitro*. We recorded the epidural ECoG activity on the surface of rhesus macaque cortex while they performed a saccadic task. The mesh PI electrode showed good contact with the brain surface, as evaluated by visual inspection and an electrical contact test with an agarose brain model. Classification analysis of left and right saccadic movements showed accuracies of about 87 % for predicting the direction of saccade eye movement during two sessions. These studies demonstrates that the mesh PI electrode was flexible, contactable and can record epidural ECoG activity while maintaining close contact to the dural layer without serious biological damage and degradation of signals, which was proved by *in vivo* and *in vitro* test. And this work exemplifies the future application of for minimally invasive BCI electrode arrays based on thin film electronic approaches.



Disclosures: **D. Baek:** None. **S.K. Brodnick:** None. **D. Park:** None. **H. Kim:** None. **S. Lee:** None. **J.C. Williams:** None.

Poster

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Topic: D.18. Brain-Machine Interface

Support: DARPA RCI N66001-12-C-4025

University of Wisconsin-Madison Graduate School and the University of Wisconsin-Madison Alumni Association

Title: *In vivo* imaging of spacial and temporal propagation of neural activity after stimulation with a CLEAR microECoG array in GCaMP6f mice

Authors: *S. K. BRODNICK[1,2], J. P. NESS[2], C. R. ESQUIBEL[2], J. R. NOVELLO[2], D.-W. PARK[2], S. MIKAEL[2], D.-H. BAEK[2], F. ATRY[3], M. R. HAYAT[2], T. J. RICHNER[4], K. W. ELICEIRI[2], L. KRUGNER-HIGBY[2], R. PASHAIE[3], Z. MA[2], J. C. WILLIAMS[2];
[1]Biomed. Engin., Univ. of Madison WI, Madison, WI; [2]Univ. of Wisconsin-Madison, Madison, WI; [3]Univ. of Wisconsin-Milwaukee, Milwaukee, WI; [4]Univ. of Washington, Seattle, WA

Abstract: Currently, clinical therapies such as deep brain stimulation for Parkinson's disease and stimulation to decrease epilepsy symptoms exist without much knowledge of how the therapies work. The mechanisms by which electrical stimulation of the central and peripheral nervous system work are still poorly understood, and need to be further investigated in order to increase effectiveness in clinical studies. Electrode arrays stimulate the cortex and deeper brain structures to lessen physiological symptoms, but the extent of which brain regions are affected by the stimulation and how it propagates has not been well studied because of the previous lack of imaging and recording tools. The volume of stimulated tissue has been estimated with computer modeling, fMRI imaging, or functional behavioral tests, but not quantitatively known. We have taken advantage of the recently developed genetically modified mouse which has the green fluorescent calcium indicator GCaMP6f in subsets of excitatory neurons. This mouse line has especially fast response kinetics and therefore is an excellent model for imaging precise neuronal activity *in vivo*. We have combined our graphene based CLEAR microECoG electrode array with chronic fluorescent *in vivo* imaging of GCaMP6f mice through a cranial window. Our investigations start to characterize the extent of the volume of neural tissue that is activated through various stimulation parameters by simultaneously imaging neural activity in real-time. By using already developed computer models and data analysis techniques, these data may also be used to tease apart the various contributors to electrical stimulation effects, such as volume conduction and synaptic propagation. Further combining this with other advanced imaging techniques (OCT, multiphoton), optogenetics, and different animal disease models will create a multi-model platform for investigating the mechanisms of action of neuromodulation on various neurological disorders.

Disclosures: **S.K. Brodnick:** None. **J.P. Ness:** None. **C.R. Esquibel:** None. **J.R. Novello:** None. **D. Park:** None. **S. Mikael:** None. **D. Baek:** None. **F. Atry:** None. **M.R. Hayat:** None. **T.J. Richner:** None. **K.W. Eliceiri:** None. **L. Krugner-Higby:** None. **R. Pashaie:** None. **Z. Ma:** None. **J.C. Williams:** None.

Poster

611. Brain Machine Interface: Methods and Technology

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Program#/Poster#: 611.06/P40

Topic: D.18. Brain-Machine Interface

Title: Chronic functionality and biocompatibility assessment of an intraneural stimulating electrode in the rat sciatic nerve

Authors: *S. M. WURTH[1], M. CAPOGROSSO[1], S. RASPOPOVIC[1,3], J. GANDAR[2], Q. BARRAUD[2], A. CUTRONE[4], J. RIGOSA[1], N. KINANY[1], G. TAVERNI[4], G. COURTINE[2], S. MICERA[1,4];
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Abstract: Peripheral nerve stimulation has been shown to have the potential to restore sensory feedback after amputation in humans. However, incomplete long term stability assessment of current intraneural electrodes limits their potential for clinical applications. An ensemble of four key criteria defines the success of a stimulating peripheral nerve electrode - stability, selectivity, functionality, and biocompatibility. Here we evaluated these pivotal features for a newly developed self-opening intra-neural electrode (SELINE) using a chronic rat model. A SELINE electrode was implanted in the left sciatic nerve of 5 female Lewis rats, which also received bipolar electrodes into ankle muscles to record electromyographic activity. Weekly evaluations of muscle recruitment curves in response to electrical stimulation through each of the ten active sites of the SELINE implant demonstrated the stability of charge delivery and muscle recruitment selectivity after three to four weeks post-implantation, and for a duration of 4.5 months. The selectivity of the electrodes allowed the preferential recruitment of flexor versus extensor muscles in all the implanted rats. To demonstrate the functionality and controllability of this selective muscle activation, we developed a closed-loop control system whereby real-time adjustment of stimulation frequency through selective electrodes achieved high fidelity control of ankle kinematics and the produced force. Immunohistochemistry of the chronically implanted

nerves revealed a loss of myelin and axons around the implant site. In all 5 rats, we also observed a layer of fibroblasts and an accumulation of multi-nucleated cells that encapsulated the implant. The high degree of muscle activation selectivity and functionality of the long term SELINE implants provides promising perspectives for chronic therapeutic applications. In light of the stability of these results, the impact of chronic intraneural implants on the surrounding neural tissue is undergoing further evaluations to understand the relationship between tissue response and electrode functionality and thereby aid a translation into clinics.

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Poster

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Support: Fondation de l'Avenir

Fondation Philanthropique Edmond J. Safra

Fondation Nanosciences

Fondation Motrice

French National Research Agency

Title: A new ECOG-based BCI system based on WIMAGINE® a fully implantable recording device for human applications

Authors: *F. SAUTER-STARACE, G. CHARVET, C. MESTAIS, M. FOERSTER, A. LAMBERT, N. TORRES-MARTINEZ, T. COSTECALDE, D. RATEL, T. AKSENOVA, A.-L. BENABID;
DRT/CLINATEC, French Alternative Energies and Atomic Energy Comm, Grenoble Cedex 9, France

Abstract: Our team has developed a fully implantable device called WIMAGINE®[i] to record ElectroCorticoGrams (ECoG) as a part of a Brain Computer Interface (BCI) platform to be used

by quadriplegic subjects[ii] to control effectors with a large number of degrees of freedom, such as a 4-limb exoskeleton. Innovative ECoG signal decoding algorithms will allow self-paced control of the exoskeleton by decoding the subject's brain activity. The implant consists of an array of 64 biocompatible epidural electrodes fixed under a titanium housing the electronic boards, and two antennae for wireless transmission of data and remote power supply. For this purpose, our team designed and handled the implant manufacturing according to ISO 13485, as well as qualification tests according to the European directive 2007/47/EC and ISO standards (risk analysis ISO 14971, ISO 45502 for electrical and mechanical safety of implantable devices and EN 60601-1 for electrical safety and electromagnetic compatibility of the external unit). Long-term biocompatibility abides by the ISO 10993 requirements, in particular the local tolerance and systemic effects after 26 weeks contact duration in animals. The clinical procedure and the investigator files were submitted to the French authorities (ANSM) and Ethical committee to get approval for the BCI clinical trials with quadriplegic subjects. Other neurological applications requiring wireless ECoG recording such as epilepsy or post stroke rehabilitation can be addressed. The project is partially supported by French National Research Agency (ANR-Carnot Institute), Fondation Motrice, Fondation Nanosciences, Fondation de l'Avenir, and Fondation Philanthropique Edmond J. Safra. Endnotes [i] Mestais, C., Charvet, G., Sauter-Starace, F., Foerster, M., Ratel, D., & Benabid, A. L. (2015). WIMAGINE®: Wireless 64-channel ECoG recording implant for long term clinical applications. *Neural Systems and Rehabilitation Engineering*, IEEE Transactions on (Volume: 23, Issue: 1), DOI: 10.1109/TNSRE.2014.2333541

ii Eliseyev A., Aksenova T., Mestais C., Benabid A-L., et al., CLINATEC BCI platform based on the ECoG-recording implant WIMAGINE and the innovative signal-processing to control the exoskeleton EMY: preclinical results, *EMBC, 36th Annual International Conference of the IEEE*, 2014, http://dx.doi.org/10.1109/EMBC.2014.6943817

Disclosures: **F. Sauter-starace:** None. **G. Charvet:** None. **C. Mestais:** None. **M. Foerster:** None. **A. Lambert:** None. **N. Torres-Martinez:** None. **T. Costecalde:** None. **D. Ratel:** None. **T. Aksenova:** None. **A. Benabid:** None.

Poster

611. Brain Machine Interface: Methods and Technology

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Program#/Poster#: 611.08/P42

Topic: D.18. Brain-Machine Interface

Support: Dutch Technology Foundation STW, number 12803

ERC Advanced Grant iCONNECT, number 320708

Title: Additional information from connectivity may improve classification in ECoG based Brain-Computer Interfaces

Authors: *E. J. AARNOUTSE, S. BROLSMA, Z. V. FREUDENBURG, N. F. RAMSEY; Brain Ctr. Rudolf Magnus, Utrecht, Netherlands

Abstract: In a permanent, implanted Brain- Computer Interface (BCI), classification of users intent must be held to a higher standard than in a laboratory setting. For example, the minimization of false positives is as important as detecting true positives (Torres Valderrama et al. 2012). We investigated whether information on the communication between two areas with distinct brain function can improve classification. Two brain functions were evaluated for BCI, in six patients scheduled for epilepsy surgery: working memory (activates dorsolateral prefrontal cortex; DLPFC) and motor (activates motor cortex; M1) BCI. A week before resection ECoG grids were implanted. In the following week they performed two screening tasks to locate DLPFC and M1: a counting back task (steps of 7) and a fingertapping task. All trials alternated with rest trials. They also performed a BCI task with visual feedback: moving a cursor in the vertical direction by either counting backwards or fingertapping for up, and active resting for down. We selected bipolar electrodes over DLPFC and M1 on the basis of significant covariance with the appropriate screening task. We than calculated Granger causality (GC) in the high gamma band between DLPFC and M1 electrodes for each of the tasks. Significance was tested with a bootstrap method. During the working memory BCI task GC was found from DLPFC to M1, whereas during the working memory screening task no GC was found. Both during the motor screening task and the motor BCI task GC from M1 to DLPFC was found, but only during motor BCI GC from DLPFC to M1 was found. Thus, we find that feedback of brain signals increases GC from DLPFC to M1, for both WM and motor BCI, as compared to the screening tasks. These results point in the direction of feedback causing a general top down effect, for example from a third frontal area. The results suggest that the activity of two areas with distinct function combined may improve BCI classification, notably reducing false positives. These results may inspire strategies for better classification in BCIs using one extra bipolar electrode.

Disclosures: E.J. Aarnoutse: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research is funded by the Dutch Technology Foundation STW, in project nr 12803 with co-funding from Medtronic Europe. **S. Brolsma:** None. **Z.V. Freudenburg:** None. **N.F. Ramsey:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research is funded by the Dutch Technology Foundation STW, in project nr 12803 with co-funding from Medtronic Europe.

Poster

611. Brain Machine Interface: Methods and Technology

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Program#/Poster#: 611.09/Q1

Topic: D.18. Brain-Machine Interface

Support: DFG, grant number EXC 1086

Title: A cost-efficient method for impedance reduction of neural microelectrodes by nanostructured platinum

Authors: *C. BOEHLER, M. ASPLUND;
Dept. of Microsystems Engin. (IMTEK), Albert-Ludwigs-University, Freiburg, Germany

Abstract: Micro-sized electrodes enable highly sensitive communication at the neural interface with superior spatial resolution and thus provide excellent possibilities for the exploration of basic neurological functions *in vivo*. Such small electrodes however suffer from high electrical impedance and low signal to noise ratio which results in adverse effects on their recording/stimulation performance. In order to overcome this problem, a nanostructured platinum coating with superior porosity was introduced as add-on functionalization for impedance reduction of small electrodes. In contrast to the fabrication process of platinum black our approach does not rely on the usage of cytotoxic components thus making it suitable for biomedical applications. The realization of the Pt-grass coating is performed via a chemical reduction process using chloroplatinic/formic acid and allows batch fabrication as well as individual site modification on larger electrode arrays. Electrochemical impedance spectroscopy (EIS) of the grass-like nanostructure displayed a reduction in impedance by almost two orders of magnitude compared to untreated platinum samples. Similarly, the charge storage capacity (CSC) and the charge injection capacity (CIC) could be substantially increased by factor 40 and 20, respectively, by implementing the Pt-nanograss coating. Biocompatibility of the nanostructured film was assessed by elution and direct contact tests using the human neuroblastoma cell line SH-SY5Y and results proved that the nanostructures were non-toxic. With the herein proposed nanostructured platinum, we were able to reduce the impedance of microelectrodes to limits below what could be reached for electrode materials like IrOx or PEDOT. This allows for a reduction of the electrode area to 1% of the untreated electrode site, while retaining equal electrical properties, which consequently offers substantially improved spatial resolution in neural recordings. The simple deposition technique further provides the opportunity to apply the impedance reduction coating to virtually any possible electrode type and correspondingly shows great potential as a universal impedance reduction strategy. The high

CSC in combination with the strong adhesion further show the potential for use in chronic stimulation and finally demonstrate the relevance of Pt-nanograss for improving the performance of geometrically small neural electrodes.

Disclosures: C. Boehler: None. **M. Asplund:** None.

Poster

611. Brain Machine Interface: Methods and Technology

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Program#/Poster#: 611.10/Q2

Topic: D.18. Brain-Machine Interface

Support: NIH Grant MH60670-11

Title: PEDOT electroplating improves tetrode impedance stability

Authors: *B. A. GROSS[1], D. BAUER[1], G. R. POE[1], N. B. LANGHALS[2];
[1]Anesthesiol., [2]Section of Plastic Surgery, Dept. of Surgery, Univ. of Michigan, Ann Arbor, MI

Abstract: Micro-wire electrodes for use in single unit electrophysiology experiments are relatively affordable in comparison with fabricated electrodes (e.g., silicon-based electrodes). Tetrodes, consisting of four electrically-isolated micro-wires bound together, are used by many researchers due to their ability to identify and classify action potentials arising from several individual neurons in densely populated neural regions, such as the hippocampus. When the target population of neurons is in a small volume of brain tissue, several individual neurons can be recorded from even if only a couple of tetrodes in a bundle reach their target. Tetrodes are commonly constructed using polyimide-insulated nichrome wire that is electroplated with gold at the recording sites before implantation into the brain. The impedance values after initial gold-plating vary greatly across several sites in the fabrication of a given batch of tetrodes and increases significantly over hours to days prior to implantation. Our goal was to produce tetrodes with lower, more uniform, and more stable impedance values than the standard gold-plated nichrome micro-wire tetrodes without significantly increasing the labor involved in fabrication. Based on several studies demonstrating the advantages of coating poly(3,4-ethylenedioxythiophene) (PEDOT) onto implantable micro-electrodes, we chose to electroplate this conducting polymer onto the gold-plated recording sites of our micro-wire tetrodes. Arrays of 8 to 16 tetrodes (32-64 electrode sites) were constructed using nichrome wire. Electrode sites were individually electroplated by placing in a gold ionic solution and applying a potential to the individual electrodes sites for 5 seconds. Then sites were connected to a Gamry potentiostat to

polymerize an EDOT monomer solution containing poly(styrenesulfonate) counter-ions using a 500 pA current for 250 seconds per site. Impedance measurements immediately after plating were significantly lower and less variable than gold-plating alone when compared at several electrophysiologically-relevant frequencies between 1 Hz and 10 kHz (p values < 0.0001). In addition, PEDOT improved the stability of the impedance at each site as compared to gold-plating alone. Our results suggest that PEDOT can provide significant stability and consistency improvements to standard gold tetrode sites. With little additional effort in fabrication, these improvements should lead to easier separation of spikes from individual neurons due to more consistent electrode-tissue interfaces.

Disclosures: **B.A. Gross:** None. **D. Bauer:** None. **G.R. Poe:** None. **N.B. Langhals:** None.

Poster

611. Brain Machine Interface: Methods and Technology

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Program#/Poster#: 611.11/Q3

Topic: D.18. Brain-Machine Interface

Title: The foreign body response to the Utah Slant Electrode Array in human peripheral nerve

Authors: ***M. B. CHRISTENSEN**[1], H. A. C. WARK[1], D. T. HUTCHINSON[2], P. A. TRESCO[1];
[1]Bioengineering, [2]Orthopaedics, Univ. of Utah, Salt Lake City, UT

Abstract: Microelectrodes have been investigated for stimulation and recording of peripheral nerves for well over half a century. Research with peripheral nerve electrodes has resulted in a number of clinical applications, including respiratory pacing, sacral nerve stimulation for urinary and fecal management, and peroneal nerve stimulation for the treatment of foot-drop. More recently, microelectrodes, including the Utah Slant Electrode Array (USEA), have been investigated for the control of neuroprosthetic devices. However, studies evaluating the foreign body response (FBR) to penetrating arrays in humans have yet to be conducted. Therefore, we evaluated the FBR to USEA implantation in median and ulnar nerves. To this end, USEAs (Blackrock Microsystems, Salt Lake City, UT) were implanted into the ulnar and/or median nerves of two patients with previous amputations. Following a 28-day implantation period, nerves were removed from the patients and immersion fixed in 4% paraformaldehyde in PBS. Electrodes were then dissected free from the nerves which were then equilibrated in a 30% sucrose solution and sectioned through the implantation site using a crysostat. Sections were placed in blocking solution overnight, and incubated overnight with primary antibodies against

MAC387 for macrophages or NF200 and S-100β for axons and myelin identification, respectively. Sections were then washed, incubated with the appropriate secondary antibodies plus DAPI, and washed again before mounting. Retrieved arrays were stained using similar methods for antibodies against MAC387. Final images were obtained by montaging multiple image fields. MAC387+ cells were observed covering the surface of all retrieved devices, similar to previous studies examining USEAs implantation in animals. Longitudinal sections showed minimal disruption of nerve fibers around electrode tracks, with no evidence of any significant loss of nerve fibers or demyelination in the implantation area other than those damaged initially at the time of insertion. Sagittal and cross-sections revealed that a relatively small percentage of the nerve was penetrated by the array. Further, cross-sections provided evidence that the array, particularly the side of the array with longer electrodes, may have migrated out of the endoneurial tissue over the indwelling period. These results suggest that while the USEA can effectively penetrate into endoneurial tissue without significant loss of axons or demyelination to function as a neuroprosthetic controller, further efforts should be made to maintain implant location over time in order to enhance its effectiveness as a neuroprosthetic interface device.

Disclosures: **M.B. Christensen:** None. **H.A.C. Wark:** None. **D.T. Hutchinson:** None. **P.A. Tresco:** None.

Poster

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Program#/Poster#: 611.12/Q4

Topic: D.18. Brain-Machine Interface

Support: NIH R21 NS088737 01

Title: ECM coatings reduce the FBR to chronically implanted microelectrode arrays

Authors: ***M. POLEI**, R. OAKES, J. SKOUSEN, P. A. TRESCO;
Bioengineering, Univ. of Utah, Salt Lake City, UT

Abstract: Microelectrode recording arrays have provided volitional control of prosthetic devices by using recorded neuronal activity from single or small populations of isolated neurons. However, such devices perform inconsistently over long indwelling periods, presumably due in part to the foreign body response (FBR). Specifically, we have shown that blood-brain barrier (BBB) leakiness and astrogliosis correlate with reduced recording performance.1 To improve biocompatibility, we have been examining the utility of hemostatic coatings to limit the initial

blood loss and reduce the FBR. To test this hypothesis, we have coated single-shank and high-density electrode arrays with Avitene™, an FDA-approved collagen hemostat, or cell-derived extracellular matrix (ECM), and examined the tissue damage and FBR following implantation into the motor cortex of male Sprague Dawley rats.open-cell polyurethane foams were fabricated, pretreated with fibronectin, seeded with primary astrocytes and cultured for several weeks.2 The cells and polymer were removed using a weak aprotic solvent and the remaining cell-derived material was rinsed in DI water and lyophilized. Planar single shank Michigan type electrodes or 4x4 UEAs were coated with acid solubilized ECM solutions by repetitive dip coatings using a sterile process. Coated electrodes and uncoated controls were implanted stereotactically in the motor cortex of adult male Sprague-Dawley rats. After a chronic indwelling period, animals were transcardially perfused and fixed with 4% paraformaldehyde. The brains were then sectioned and FBR characterized using biomarkers for macrophage activation (CD68), blood-brain barrier dysfunction (IgG), gliosis (GFAP) and implant-associated neuronal death (NeuN).3Eight weeks after implantation, Avitene™ and ECM coated single-shank electrodes showed reductions in the intensity and spatial distribution of glial fibrillary acid protein (GFAP) and IgG immunoreactivity but not CD68. More extensive analysis is ongoing and will be reported at the meeting.Our results show that such ECM coatings may be a useful tool for reducing some elements of the FBR to these and other such devices chronically implanted in the central nervous system. Current research is focused on investigating underlying mechanisms of action. References: 1. Nolta, N., Tresco P.A, et al., Biomaterials, 2015, 53, pp. 753-762 2. Wolchok J.C. and Tresco P.A., Biomaterials, 2010, 31, pp. 9595-9603 3. Skousen J.L. et al., Prog. Brain Res., ¬¬¬2011, 194, pp. 167-180

Disclosures: **M. Polei:** None. **R. Oakes:** None. **J. Skousen:** None. **P.A. Tresco:** None.

Poster

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Program#/Poster#: 611.13/Q5

Topic: D.18. Brain-Machine Interface

Support: MEXT/JSPS KAKENHI 26282162

MEXT/JSPS KAKENHI 15K12576

Title: Artifacts reduction with a simple filter for multichannel implantable neural interfaces

Authors: *O. FUKAYAMA, K. MABUCHI;
The Univ. of Tokyo, Tokyo, Japan

Abstract: Implantable neural interfaces have become a powerful tool to observe information flow inside the body both for scientific purposes and clinical uses. However, they have suffered from artifacts caused by body movements or noise sources nearby the recording site. Although many sophisticated noise reduction methods have been proposed, methods extracting components such as PCA or ICA may prejudice a physical context of the recorded signals, while machine learning methods such as ANN or GA tend to cause unintended effect on the information that the signal conveys. In this work, we propose a simple temporal filter design for multichannel implantable neural interfaces based on frequency bands limitation preserving the signal properties. The basic idea of our method is to remove common-mode components caused by signals in non-target channels from the signals observed in the target channel. First, by-channel immediate weights are determined according to a ratio of a cross-correlation coefficient between the target and non-target channels and an auto-correlation on the target channel. Then, we formed an estimation of the true source as a convolution of the weighted summation of the non-target signals and a finite impulse response (FIR) by solving a Wiener-Hopf equation. The method was tested with the extracellular neural signals recorded in the cortical brain and the sciatic nerve fibers of a behaving rat, and the vagal nerve of an anesthetized goat which had an artificial heart device implanted in its chest cavity. In the case of recording the cortical brain of a rat, the method has reduced motion artifacts contaminating the neural signals recorded with wire electrodes. Another application to the sciatic nerve signals has suppressed the influence of EEG signals caused by muscles near the chronically implanted cuff electrodes during the free movements. The method was also applied to an acute recording of the vagal nerve signals of a goat with an artificial heart (AH) device, which enabled an observation of a neural-oriented signals in spite of the presence of strong AH motor noises.

Disclosures: O. Fukayama: None. **K. Mabuchi:** None.

Poster

611. Brain Machine Interface: Methods and Technology

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Program#/Poster#: 611.14/Q6

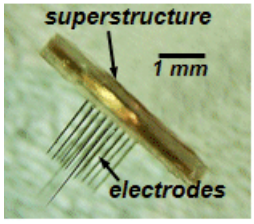
Topic: D.18. Brain-Machine Interface

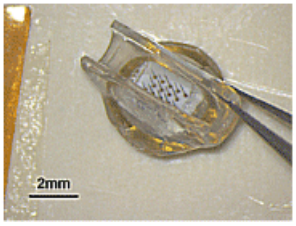
Support: TATRC Grant W81XWH-12-1-0394

Title: Wireless floating microelectrode array (WFMA)for neural stimulation

Authors: *P. TROYK[1,2], S. COGAN[3], M. ROMERO-ORTEGA[3], M. BAK[4], S. BREDESON[1]; [1]Illinois Inst. Tech., Chicago, IL; [2]Sigenics, Inc, Chicago, IL; [3]Univ. of Texas, Dallas, TX; [4]MicroProbes for Life Sci., Gaithersburg, MD

Abstract: Neural interfaces for stimulation of the central and peripheral nervous system are being proposed for numerous research and neural prosthesis devices. Wires and cables that connect to electrode arrays, and other structures placed on or near neurons and axons, often cause short-lived viability. For chronically-implanted devices, wires and transcutaneous connectors are often the primary cause of failure. Functionally, placing stimulation electronics physically close to the stimulating electrodes avoids crosstalk between adjacent electrodes. Called the Wireless Floating Microelectrode Array, (WFMA) this self-contained implantable stimulation device contains 16 iridium metal wire electrodes within a ceramic platform. An application-specific-integrated-circuit (ASIC), and power/communication coil, are placed on the top side of the ceramic platform, resulting in an assembly of 5mm diameter x 0.5mm thickness. Powering and communication with the ASIC takes place through a transcutaneous inductive link, without wires or connectors, via an extracorporeal telemetry controller (TC) that provids the magnetic power and the computer-based command/telemetry interface. The area and length of the electrodes are independently configurable. The first generation of WFMA is being tested in rodent sciatic nerve experiments. WFMAs implanted on the sciatic nerve have been stable and shown to produce differentiated stimulation of limb muscles over a period of greater than 150 days (experiment ongoing), with 3cm of separation between the implanted WFMA and the external TC. Stimulation thresholds and reverse telemetry of electrode waveshapes have been documented. In contrast, for the same animal model, wired arrays with percutaneous connectors remained fully functional for less than one month.





Disclosures: **P. Troyk:** A. Employment/Salary (full or part-time):; Sigenics, Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sigenics, Inc. **S. Cogan:** None. **M. Romero-Ortega:** None. **M. Bak:** A. Employment/Salary (full or part-time):; MicroProbes for Life Sciences. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); MicroProbes for Life Sciences. **S. Bredeson:** None.

Poster

611. Brain Machine Interface: Methods and Technology

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Support: This work was sponsored by The Defense Advanced Research Projects Agency (DARPA) Microsystems Technology Office (MTO), under the auspices of Dr. Jack W. Judy and Dr. Douglas Weber Pacific grant No. N66001-11-1-4013.

Title: Evaluation of systemic and histological changes using accelerated failure studies in mice implanted with intracortical device

Authors: J. GAIRE, *K. J. OTTO;
Univ. of Florida, Gainesville, FL

Abstract: Intracortical microelectrode devices provide a brain machine interface capable of targeting very small populations of neurons with a potential to treat many neurological disorders. These penetrating devices generally perform well for a short duration but fail to record or stimulate reliably for chronic time putatively due to reactive tissue response (RTR). The RTR though suggested to be one of the major failure modes, has not been yet firmly established as a cause for device failure. In this study, we evaluated the changes in systemic markers of inflammation and histological changes in animals implanted with silicon microelectrodes and received either lipopolysaccharide (LPS) or Dexamethasone (Dex). We dip-coated implanted devices with LPS, a bacterial endotoxin, and injected Dex systematically. The panel of pro-inflammatory markers were analyzed using multiples plates (Mesoscale Discovery) and histological changes using device capture histology (DCHIST) [1, 2]. In our preliminary results, we did not see any significant increase at the systemic levels of pro-inflammatory marker in implanted animals after one week. This observation could be due to 1) the longevity of the 1 week time point as opposed to acute time points (hours) after implantation, 2) the systemic method of assessment instead of local assessment, and 3) small number of animals used. We chose to measure the cytokines systemically so that the histological assessment of the tissue surrounding the implant can be performed from the same animal. The group of animals that received both the implant and LPS showed increased levels of pro-inflammatory marker as compared to group that received the implant only. However, the increase was minimal and could be due to a small amount of LPS that went into the brain. In conclusion, our study indicates that collecting blood samples at multiple time points from the same animal will be useful in gathering data that can be corroborated with histological and electrophysiological findings to make meaningful conclusions from the same subject. The use of pro- and anti-inflammatory substances, like LPS and Dex, in tandem with new imaging techniques will help to discern if the causality between inflammation and device performance exists.

Disclosures: **J. Gaire:** None. **K.J. Otto:** None.

Poster

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Topic: D.18. Brain-Machine Interface

Support: Defense Advanced Research Projects Agency contract N66001-10-C-4056

Title: Does precise pulse timing affect the perception of intracortical microstimulation?

Authors: ***T. CALLIER**[1], H. P. SAAL[1], E. W. SCHLUTER[1], F. V. TENORE[2], S. J. BENSMAIA[1];
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Abstract: Intracortical microstimulation (ICMS) can be used to deliver naturalistic and intuitive sensory feedback in upper-limb neuroprostheses. One way to evoke graded sensations is to vary the stimulation amplitude. Another way is to vary the timing of the stimulation pulses. Indeed, the precise spiking timing of neuronal responses has been shown to carry information and shape perception. For example, skin oscillations, such as those evoked when touching a textured surface, are encoded in primary somatosensory cortex (S1) in two ways: the strength of the response (firing rates) tracks the amplitude of the vibrations, while the precise spike timing of the response signals their frequency composition. In theory, varying ICMS pulse frequency and amplitude should thus have distinct perceptual consequences. In a landmark study, Romo and colleagues have shown that monkeys are able to distinguish changes in ICMS pulse frequency at low frequencies (< 50 Hz). However, the timing of cortical responses has been shown to carry information up to much higher frequencies. In the present study, we ask whether changes in ICMS frequency produce distinguishable percepts across a wide range of frequencies. To this end, we train Rhesus macaques to discriminate the frequency of vibrations delivered to the hand, with frequencies ranging from 50 to 400 Hz. The vibratory amplitude varies randomly from trial to trial so that the animals cannot rely on intensity cues to make the frequency discrimination judgments. Once the animals are trained on the task, we have them perform the same task based on ICMS delivered to S1 through chronically implanted electrode arrays. We then assess the animals' ability to generalize from the mechanical to the electrical version of the task to infer the degree to which the two tasks are perceptually analogous. Our preparation allows us to probe causally the importance of precise spike timing in S1, and to determine the limits of ICMS with respect to pulse timing.

Disclosures: **T. Callier:** None. **H.P. Saal:** None. **E.W. Schluter:** None. **F.V. Tenore:** None. **S.J. Bensmaia:** None.

Poster

611. Brain Machine Interface: Methods and Technology

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Program#/Poster#: 611.17/Q9

Topic: D.18. Brain-Machine Interface

Title: Effects of stimulation frequency on the excitability of central nervous system during functional electrical stimulation

Authors: *H. SUZUKI[1], T. ONO[4], E. YAMADA[4], S. KASUGA[2], J. USHIBA[3];
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Abstract: Functional Electrical Stimulation (FES) to the paralyzed limb after stroke is considered to induce adaptive plasticity in the motor system through exciting afferent and efferent pathways. The stimulation frequency most commonly used in studies investigating FES-based rehabilitation of paralysis is relatively low (20-80 Hz; Fujiwara et al. Neurorehabil Neural Repair 2009), while higher frequency (100 Hz) stimulation is suggested to excite central nervous system (Collins et al. J Neurosci 2001). In order to clarify optimal stimulation frequency for clinical purpose, relationships between stimulation frequency and the excitability of central nervous system need to be investigated. In this study, we sought to identify a stimulation parameter adequate to excite afferent and efferent pathways by comparing high-frequency-FES (HF-FES) and low-frequency-FES (LF-FES). In eight neurologically normal participants, we acquired functional magnetic resonance images during HF-FES (100 Hz) and LF-FES (20 Hz) whose intensities are adjusted to produce 45-degree of wrist dorsiflexion. Only HF-FES significantly activated contralateral primary motor cortex (M1) and contralateral primary somatosensory cortex ($P < 0.001$ unc.). To test whether this M1 activation results in the excitation of the exact efferent pathways, in the next experiment we investigated cortical excitability during HF-FES and LF-FES by using transcranial magnetic stimulation (TMS) in ten neurologically normal participants. We identified TMS intensities evoking more than 2-degree change of wrist dorsiflexion while applying HF-FES and LF-FES whose intensities are adjusted to produce 30-degree of wrist dorsiflexion. The identified TMS intensities during both HF-FES and LF-FES were lower than those during rest ($P < 0.001$), and the intensities during HF-FES

were lower than those during LF-FES ($P < 0.05$) in all subjects. Our results suggest that HF-FES activates both the afferent and efferent sensorimotor pathways, therefore this frequency might be useful in FES-based interventions which aim to improve the excitability of central nervous system. The current findings may also be applicable to electrical stimulation as sensory feedback of Brain-Machine Interface-based stroke rehabilitation.

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Poster

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Program#/Poster#: 611.18/Q10

Topic: D.18. Brain-Machine Interface

Support: ERC-2012-AdG 320708-iCONNECT

Title: Large scale group analysis of spectral features in electrocorticography

Authors: ***Z. V. FREUDENBURG**[1,2], R. VAN DER SPEK[2], M. J. VANSTEENSEL[2], E. J. AARNOUTSE[2], N. F. RAMSEY[2];
[1]UMC Utrecht-Rudolf Magnus Inst., Utrecht, Netherlands; [2]Brain Ctr. Rudolf Magnus, Univ. Med. Ctr. Utrecht, Utrecht, Netherlands

Abstract: Spectral features in human brain electrophysiology have been extensively studied in relation to human brain function, and have proven robust enough for use in clinical diagnostic practices and online closed-loop direct cognitive control of a computer. Lower frequency bands have been associated with various functions in EEG, such as the alpha, theta and mu bands for visual attention, working memory and motor action respectively. Functional significance of these bands appears to be confined to specific regions of the brain, but the exact source and extent of involved cortex is unclear due to the limited sensitivity of EEG. Electrocorticography (ECoG) allows for detailed mapping of electrophysiological signals across the human cortex with high topographical precision since each electrode measures from only the cortical tissue with which it is in direct contact. ECoG has the added benefit of being sensitive to high gamma frequencies, which have been closely linked to increased neuronal spiking and BOLD signal increases [Nir et al. 2007, Goense et al. 2008], allowing ECoG to relate low frequency patterns to these other domains. In this study we addressed the question whether the cortex exhibits a topographical distribution of function-related low frequencies. For this we studied ECoG data from 11 patients

who performed multiple cognitive and motor tasks. Each subject had 64-117 non-noisy electrodes, and performed up to 12 tasks, bringing the total number of datasets to 151 and ECoG measurements to 14,154. ECoG was recorded with the standard clinical grids used in pre-resection epileptic focus localization. Anatomic localization of electrodes was done with the help of pre-surgical MR and post-implant CT scans. Amplitude variance during the tasks was used as an indication of the functional significance. For each electrode measurement PCA was performed on the amplitude response of 66 frequencies exponentially sampled from 1-135Hz and the top 2 components were used as its canonical spectral feature. The measurements were then clustered using a variant of Affinity Propagation [Frey et al. 2007] into 13 groups of similar canonical features. The results show that 1) despite being defined naively without task labels, the canonical features that bind each cluster display bands responses highly comparable to those defined using functional contrast, 2) the clusters of like spectral features are anatomically specific but not subject or cognitive task specific. This suggests that different regions exhibit functionally relevant different spectral features. It remains to be seen how this distribution relates to anatomical differences between regions.

Disclosures: Z.V. Freudenburg: None. **R. van der Spek:** None. **M.J. Vansteensel:** None. **E.J. Aarnoutse:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Funded by the Dutch Technology foundation STW with co-funding from Medtronic Europe as affiliation. **N.F. Ramsey:** None.

Poster

611. Brain Machine Interface: Methods and Technology

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Program#/Poster#: 611.19/Q11

Topic: D.18. Brain-Machine Interface

Title: Investigating the effect of current flow on cortical excitability using bipolar tDCS

Authors: *V. RAWJI[1], J. C. ROTHWELL[1], S. BESTMANN[1], M. CIOCCA[2], A. ZACHARIA[3], M. BIKSON[4];
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Abstract: Question TDCS over M1 conventionally has the cathode/anode directly over M1 with a remote return electrode. However, calculations suggest that field intensity is max between the two electrodes.1 Here we ask whether tDCS to an area between two electrodes has different effects depending on the orientation of the applied field. We conducted experiments on the FDI hand area of M1 since previous work has shown that stimulation here with TMS is directionally dependent.2 Methods TMS intensity was adjusted to produce MEPs of approximately 1mV peak-to-peak amplitude. Twenty MEPs from the right FDI were collected before and after conditioning the cortex with 10min 1 mA TDCS with the TMS coil 45o to the midline. HD-tDCS (Neuroelectrics, Spain; 1mA, 10min) was delivered via circular electrodes (3.14cm2), each placed 3.5cm from the FDI hotspot. Two were positioned parallel to the TMS coil to induce either a posterior-anterior (PA-tDCS) or anterior-posterior (AP-tDCS) current across the hotspot. Two perpendicular to the coil induced a mediolateral current (ML-tDCS). This protocol involved three sessions: (1) ML-tDCS, (2) PA-tDCS and (3) sham stimulation, all with PA TMS (n=15). In experiment 2 (n=20), we reversed the polarity of PA-tDCS (AP-tDCS) and repeated parameters from experiment one. Experiment 3 (n=14) investigated the effects of PA-tDCS on PA and AP TMS. To complete the permutations, we tested the effect of AP-tDCS on AP TMS pulses (n=14). Results Modelling: We found clear differences between electrical fields induced by PA and ML tDCS Experiment 1: PA-tDCS significantly reduced M1 excitability compared to ML (p=0.006) and sham stimulation (p=0.005) but ML stimulation showed no significant change in M1 excitability compared to sham (p=0.46). These were all under PA TMS. Experiment 2: Comparison between PA-tDCS and AP-tDCS, using PA TMS showed no significant difference. Experiment 3: Using PA-tDCS, we showed a significant difference between post-stimulation effects between PA and AP TMS (p=0.024). Experiment 4: Using AP-tDCS, we found no significant difference between post-stimulation effects between PA and AP TMS. Variability: We tested PA-tDCS with PA TMS in 22 subjects, with 15 of these being tested twice. The interclass correlation was found to be 0.68, indicating moderate-strong reproducibility. Conclusions We show that tDCS displays a clear element of anisotropy, with particular emphasis on the PA-tDCS orientation. Further investigations are needed to elucidate the physiological mechanisms of this anisotropy.

Disclosures: V. Rawji: None. **J.C. Rothwell:** None. **S. Bestmann:** None. **M. Ciocca:** None. **A. Zacharia:** None. **M. Bikson:** None.

Poster

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Program#/Poster#: 611.20/Q12

Topic: D.18. Brain-Machine Interface

Support: NIH-R01 MH092926

Title: Direct current stimulation modulates bidirectional synaptic plasticity

Authors: *G. KRONBERG[1], M. BRIDI[2], T. ABEL[2], L. C. PARRA[1];
[1]Biomed. Engin., The City Col. of New York, New York, NY; [2]Biol., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Transcranial direct current stimulation (tDCS) is an emerging therapeutic technique being explored for the treatment of a wide range of neurological disorders. Despite its rapid adoption, little is known about the cellular mechanisms that underlie long-term tDCS outcomes. To elucidate these mechanisms, we applied direct current stimulation (DCS) during synaptic plasticity induction in rat hippocampal slices. DCS biased synaptic plasticity towards potentiation, i.e. enhanced long-term potentiation (LTP) and attenuated long-term depression (LTD), when applied during plasticity-inducing synaptic activity. However, if concurrent synaptic activity was too weak to induce plasticity, DCS had no effect on the strength of synapses. Our results provide a mechanism for tDCS to enhance memory storage, by facilitating LTP when applied during synaptic plasticity induction, as presumably occurs during the performance of a cognitive task. Moreover, these results provide a mechanism for tDCS to be functionally specific, selectively affecting synapses that are undergoing plasticity. We show further that the effects of DCS vary with the dendritic location of synapses (i.e. apical or basal) and are NMDA receptor dependent, supporting the notion that DCS modulates synaptic plasticity by modulating dendritic membrane potential. Taken together, our results motivate the application of tDCS during plasticity-inducing cognitive tasks and draw attention to the influence of dendritic membrane polarization in determining long-term tDCS outcomes.

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Poster

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Program#/Poster#: 611.21/Q13

Topic: D.18. Brain-Machine Interface

Support: NIH EB006433

Title: Different learning processes of multichannel versus small channel configuration for online brain-computer interface

Authors: *J. MENG, S. ZHANG, A. BEYKO, T. HANSON, B. HE;
Univ. of Minnesota, Minneapolis, MN

Abstract: Motor imagery based brain computer interfaces (BCI) using electroencephalography (EEG) have shown promising results in the control of virtual or real objects, during which subjects can learn to modulate brain rhythms. BCI studies commonly employ a small channel configuration, known as a large Laplacian, which uses the same two electrodes/channels together with surrounding channels. A more recent approach is the multichannel configuration, which can utilize more EEG electrodes than the small channel configuration. With additional electrodes and different online decoding algorithms, better performance and new learning processes may be expected. One challenge is that additional channels lead to higher inclusion of both task-related and -unrelated information, and thus may obfuscate the task-related information and affect the efficiency and stability of learning processes. This study aimed to compare the learning processes between the two configurations (multichannel vs. small channel) by evaluating the average online performance across several sessions. BCI naïve subjects were recruited to participate in the experiments and were randomly distributed into two groups. Each group performed 1D online cursor control with one configuration for 3 sessions and then crossed over to the other configuration for the remaining 2 sessions. The experimental results revealed that the multichannel configuration exhibited significantly better performance initially within naïve subjects, though it did not lead to a congruent improvement in long-term learning. In contrast, the small channel configuration displayed a slow and steady improvement on average across all sessions. The results indicate that learning may initially involve a larger brain area and multichannel configuration and corresponding algorithm can use information from a broader range of brain regions to achieve a better initial performance; whereas, as learning progresses, both methods approach equivalent performance level and the two electrodes (C3 and C4) above the motor cortex becomes sufficient for the subjects to learn to control the cursor or objects. This might explain why the multichannel configuration can decode motor imagination better initially, while small channel improved after a long-term learning period. This work was supported in part by NIH EB006433.

Disclosures: **J. Meng:** None. **S. Zhang:** None. **A. Beyko:** None. **T. Hanson:** None. **B. He:** None.

Poster

611. Brain Machine Interface: Methods and Technology

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Program#/Poster#: 611.22/Q14

Topic: D.18. Brain-Machine Interface

Title: Methods for detecting speech articulation events from single channel recordings of the speech cortex

Authors: M. MCCURRY[1], P. KENNEDY[2], *M. CLEMENTS[1];
[1]777 Atlantic Drive, Georgia Inst. of Technol., Atlanta, GA; [2]Neural Signals Inc., Duluth, GA

Abstract: Identifying speech articulation from electrode recordings of individuals with restricted articulation is an area of ongoing research. Acquiring data for this task can be difficult and the amount is often quite small. Additionally, comparisons across patients with different conditions is often nearly non-existent. To provide a point of comparison an unimpaired individual (PK) was implanted with 4 electrodes in his speech motor cortex. Over 15 days recordings were made using this set of electrodes in an effort to observe activity during articulation. These recordings focused on creating a series of sections of rest, vocalization, subvocalizations, and coarse muscle movement in the mouth. This work focuses on identifying the characteristics of vocalization events within these recordings and finds that highly statistically significant markers can be found and extracted from the local field potentials. These markers generally occur either during a vocalization event or very shortly after the termination of the audible speech. Each marker was extracted from single electrode recordings and matched with speech recorded from a time synchronized microphone. In order to extract these events from the raw electrode signal a series of non-linear processing steps were sequentially applied. First a 3788Hz recording was converted into a spectrogram with 90% overlap and half second windows. Then areas corrupted by recording noise were removed by limiting the region of interest and eliminating the 0-64Hz band. At this stage the events could be visibly observed due to their excitatory nature, though peppering noise made extraction difficult. To correct for this a combination of median filtering and thresholding was used to denoise the signal. At this point the events were extracted via gating the overall energy and observing the central frequency at each frame of time. Some artifact elimination was performed on this representation and then the events were compared to their distance from the nearest previous audible vocalization. In recording with word and phrase based utterances the event markers appeared to coincide with audible articulation events 77%+-11.6% of the time when the chance rates were 30.2%+-7.4%. In phoneme based files, event markers appeared at chance levels. In addition to these classification rates, there were some noteworthy differences between the characteristics of the event markers when used in different words which may indicate some word or phrase specific structure. This preliminary work shows promise in extracting articulation events from the speech motor cortex, though further datasets would be required to fully characterize and utilize them.

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Poster

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Topic: D.18. Brain-Machine Interface

Support: ERC-2012-AdG 320708-iCONNECT

Title: Characterization of gamma electrophysiological response over sensorimotor cortex

Authors: ***M. P. BRANCO**, Z. V. FREUDENBURG, E. J. AARNOUTSE, M. J. VANSTEENSEL, N. F. RAMSEY;
Brain Ctr. Rudolf Magnus, Univ. Med. Ctr. Utrecht, Utrecht, Netherlands

Abstract: Gamma power activity has been recently considered as a feature for electrocorticography(ECoG)-based brain-computer interface (BCI) control. This activity (30-150 Hz) is known to be involved in several fundamental brain functions, in particular during motor execution or attempted movement. Gamma responses typically emerge as a spiky transient response time-locked to cognitive events and are commonly anatomically specific [1,2]. Wavelet-based signal analysis has been shown to be appropriate for power extraction, particularly when gamma responses are expected to show dynamics on a short temporal scale [3]. Typically, spectral analysis of the neuronal signals involves the use of a Morlet wavelets dictionary, the computational implementation of which requires the specification of at least two parameters: temporal resolution and smoothing. By varying these in a controlled manner, we can access important properties of the gamma response, such as the duration or sharpness of the gamma peaks and its smoothness or noise morphology. The characterization of such response could help to better understand the electrophysiology behind gamma responses, as well as to improve decoding strategies. We used data from 12 epilepsy patients who were implanted either with clinical or high-density ECoG grids over the sensorimotor cortex. Both impulse (button press or stimulation) and sustained (complex gestures or phonemes execution) gamma power (65-125 Hz) responses, were obtained through different combinations of temporal resolution (sampling every 0.002 to 0.1 s) and smoothing (window 0 to 3 s). The results revealed that both impulse response, characterized by maximum R2 values, and sustained cortical tasks, characterized by decoding classification accuracy, show an optimal range for gamma temporal sampling and smoothing. This range indicates that motor gamma response classification improves with a particular combination of higher temporal resolution and smoothing. Hence, we propose that in the analysis of ECoG gamma power the temporal response should be sampled at a high rate (> 1 sample/0.02s) and smoothed with a window of approximately 0.5 s. Given that

sensorimotor gamma responses tend to be quite variable and noisy, suboptimal sampling and smoothing may affect the interpretation in terms of the anatomic and temporal characteristics of underlying neuronal response. Therefore, optimization of wavelet-based power extraction methods will not only enable better decoding for BCI purposes, but also give a better understanding of the electrophysiological events underlying the gamma response. [1] Buzsáki and Wang, NS 2012. [2] Hermes ea, HBM 2012. [3] Bruns, JNM 2004.

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Poster

612. Brain-Machine Interface Grasping Devices

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Title: Dynamic iterative brain-computer interface for dexterous hand movements

Authors: ***J. WU**[1,2], N. R. WILSON[2], D. SARMA[2], V. KUMAR[3], T. M. BLAKELY[2], F. DARVAS[4], B. W. BRUNTON[5], J. G. OJEMANN[4], R. P. N. RAO[3];
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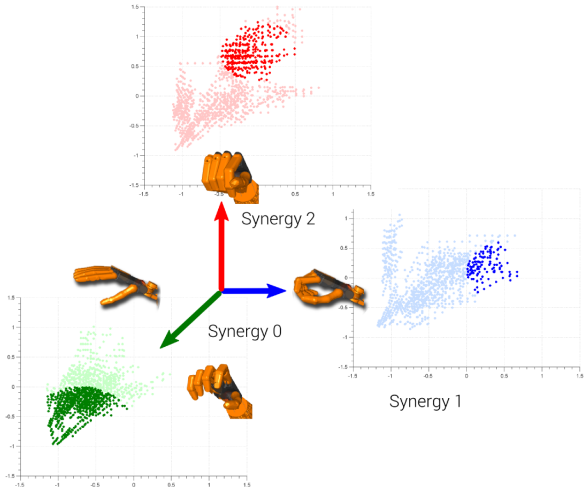
Abstract: Electrocorticography (ECoG)-based control systems for dexterous upper-body robotic prostheses have demonstrated potential to fulfill a role as implanted brain-computer interfaces (BCI) for volitional control of assistive devices. However, hand movement BCIs based on ECoG data primarily rely upon epoch-based end-point postural interpretation. One improved model of closed-loop BCI for hand prosthetics would be the incorporation of natural human control and feedback; this may be accomplished by dynamically decoding the velocity of underlying "movement primitives" multiple times a second to allow for real-time correction and adaptation.

Here we demonstrate preliminary performance of iteratively decoding ECoG sensorimotor recordings into dimensionality-reduced correlates of hand movement primitives. A variety of multi-spectral-band decoding strategies are experimentally tested on both imagined and overt movement paradigms in order to better understand the dynamics of human hand control in epileptic patients implanted with clinical (10mm spacing) and high-resolution (3mm spacing) platinum subdural ECoG grids, with differing spatial control patterns and control timing. Initial decoding tests in one implant patient (age 33, 8×8 lateral temporalparietal clinical grid) during a dynamic dwell task of a software robotic hand in three target postures (ball, handle, and pinch) in a closed loop imagined movement BCI achieved decoding accuracies of 70%, 20%, and 10% respectively, as compared to the chance at 40%, 10%, and 10%. These recordings suggest the presence of movement primitives during overt coordinated grasping and virtual hand control, and the capacity for real-time decoding of grasps from ECoG activity. Further, subject BCI performance reveals potential capability for real-time closed-loop error correction of the end-user in using decoded movement velocities to perform simulated motor tasks. We hope to significantly advance our computational understanding of human neural control of manipulation as well as ECoG-based dynamic hand prosthetics.



Dynamic decoding performance of overt movements in a two-dimensional synergy space; each dot represents a postural position every 100ms.

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Poster

612. Brain-Machine Interface Grasping Devices

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 612.02/Q17

Topic: D.18. Brain-Machine Interface

Support: R01 NS053603

Title: Initial performance is better in altered BMI decoders that preserve muscle synergies

Authors: *S. N. NAUFEL, L. E. MILLER;
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Abstract: Our lab has developed a neuroprosthetic system with potential application to spinal cord injury that uses recordings from motor cortex (M1) to "decode" intended muscle activity (EMG). We can in turn control muscle stimulation to restore voluntary grasp. Understanding the limits of a patient's ability to adapt to these imperfect decoders has become a central question in the field of Brain Machine Interfaces (BMIs). We used our unique BMI to study a monkey's ability to adapt to two types of altered decoders: one that preserved the natural synergies between muscles, and one that didn't. Ultimately the monkey was able to use the synergy-preserving decoders much more successfully than those that disrupted natural synergies. We first trained a rhesus macaque to apply isometric wrist torque, with its forearm held in the mid-prone position, to place a cursor within one of 8 targets. We recorded multi-unit activity from a 96-channel microelectrode array implanted in the hand area of M1, as well as EMG from the major wrist muscles: extensor carpi radialis (ECR), extensor carpi ulnaris (ECU), flexor carpi radialis (FCR), and flexor carpi ulnaris (FCU). We computed a "cascade" decoder made of two multiple-input, linear filters: one to decode EMG from neural activity, and a second to decode force from EMG. We designed a synergy-preserving, "rotated" decoder by substituting an EMG-to-force decoder that was trained on data collected with the monkey's forearm rotated 90 degrees to the pronated position. We also designed a "reflected" decoder in which ECR and FCR were swapped, "reflecting" their lines of action across their insertions at the wrist, and simulating an anatomically impossible configuration. In a given session we alternated blocks of the normal decoder and one of the altered decoders. The rotated decoder was the more intuitive of the two altered decoders, as the animal could initially reach three times as many targets as in the reflected case. Furthermore, after 10 days, the monkey still had not learned to reach all targets using the reflected decoder. At this point, his performance in the rotated case was similar to that during normal decoder use, and nearly five times better than the reflected performance. Notably, with the reflected decoder, the monkey could most reliably reach the target that required only ECU and FCU activity. These two muscles were unaffected by the decoder transformation. These results suggest that the user can adapt to neuron-to-muscle decoders that preserve muscle synergies much more readily than those requiring completely new synergies. However, we don't know whether even longer-term adaptation may allow non-synergistic control to be learned.

Disclosures: S.N. Naufel: None. **L.E. Miller:** None.

Poster

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Support: Doris Duke Charitable Foundation Clinical Scientist Development Award (#2011039)

Northwestern Memorial Foundation Dixon Translational Research Grant

Brain Research Foundation

Title: Distinct motor cortical representations for grasp kinematics and kinetics

Authors: *R. D. FLINT, III[1], E. W. LINDBERG[1], E. M. MUGLER[1], J. M. ROSENOW[2], M. C. TATE[2], M. W. SLUTZKY[3,4];
[1]Neurol., [2]Neurolog. Surgery, [3]Neurology, Physiology, and Physical Med. & Rehabil., Northwestern Univ., Chicago, IL; [4]Rehabil. Inst. of Chicago, Chicago, IL

Abstract: Grasping an object requires continuous control over two motor activities: isotonic movement and isometric force. The transition between these two activities has been shown to be nonlinear in terms of the muscle activity causing finger flexion. This nonlinearity suggests that movement kinematics and force may have different cortical representations, despite their common muscle origins. By contrast, cortical networks in non-human primates have been shown to be capable of rapid, task-related modulations during arm movements. The extent to which cortical representations may shift during a motor act is a question of primary interest in neuroscience. It could also inform the design of brain-maching interface (BMI) technology for restoring function to the disabled. To investigate the nature of kinematic and kinetic grasp representations in human cortex, we recorded the electrocorticogram (ECoG) of subjects from two populations: 1) patients who were undergoing monitoring for treatment of intractable epilepsy; and 2) patients who were undergoing an awake craniotomy procedure for functional mapping during tumor resection. The subjects performed both kinematic and kinetic grasp tasks involving a precision pinch movement. We decoded the continuous kinematics of the thumb and index finger joints, as well as the continuous isometric force, at each ECoG electrode using a Wiener cascade decoder of spectral features (0-300 Hz). We then represented each electrode by its cross-validated decoding accuracy for joint kinematics or force. This produced maps of cortical activation associated with the movement of each joint, and with the regulation of force. In each subject we evaluated, the kinematic representations were highly conserved across the different joints of the thumb and index finger. However, those representations were distinct from

the representation of isometric pinch force. This occurred even in a grasp task that placed an index finger pinching motion and force application directly in series. These results suggest that the kinematic and kinetic phases of hand grasp are encoded differently in the cortex.

Disclosures: R.D. Flint: None. **E.W. Lindberg:** None. **E.M. Mugler:** None. **J.M. Rosenow:** None. **M.C. Tate:** None. **M.W. Slutzky:** None.

Poster

612. Brain-Machine Interface Grasping Devices

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Topic: D.18. Brain-Machine Interface

Support: CIMIT Foundation

Title: Nerve-muscle graph chamber for amputee control of powered prostheses

Authors: *R. R. RISO[1], M. J. CARTY[2], S. G. TALBOT[2], H. M. HERR[1];
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Abstract: Powered prostheses require reliable and intuitive means for users to control the joint movements simultaneously and with minimal effort. An ideal solution is to derive the control from the user's peripheral nerves since amputee's can initiate and coordinate the requisite neural activity according to volitional intent. Moreover, sensory input (e.g. vision, vestibular, joint and cutaneous forces) can be applied automatically for corrective adjustments with minimal delays. Developers of neural interfaces still struggle with issues of stability, low recorded signal amplitudes and motor nerve selectivity. Our studies aim to mitigate these issues by developing a "nerve-muscle graft chamber" (NMGC) where the stump of an amputated nerve is grafted to a piece of autologous muscle (ca. 4mm2 x 20mm) that is placed into an isolated compartment of the NMGC. This strategy modifies the Targeted Muscle Re-Innervation (TMR) technique [Kuiken et.al., JAMA 301(6), 2009] to afford several benefits: The major advantage of transforming the neural activity into higher amplitude EMG activity to facilitate recording is retained, but the need to sacrifice the original function of a healthy host muscle to accept the grafted nerve can be eliminated by salvaging the needed muscle tissue from the amputated limb. In addition, NMGCs can be installed at the existing locations of the nerves to eliminate mobilizing nerves over long distances. With TMR, depending on the complexity of the grafted nerve, the muscle may be innervated by a mix of nerve fascicles originally targeted to multiple

other muscles. By fabricating NMGCs in a variety of sizes and numbers of muscle compartments, fascicles from a complex nerve can be mechanically divided by function and then each isolated functional group can be directed to a separate NMGC compartment. Preliminary studies at InnerSea Tech., Inc. used a dual compartment NMGC with transgenu amputated rabbits: The transected tibial and peroneal nerves were each introduced to one of the muscle slice compartments. Tri-polar electrodes in each compartment recorded independent activity from the tibial and peroneal nerves elicited by postural disturbances and volitional movements. Recorded EMG signals were robust (>100uv) and well modulated suggesting they would be adequate for graded prosthesis control. Continuation studies in our MIT laboratory involve NMGCs applied to the transected tibial n. in Ferrets. Neural activity is assessed during treadmill walking and standup tasks. NMGC designs anticipate the future addition of micro-channel nerve regeneration arrays applied proximally to allow for sensory stimulation and additional command signal acquisition.

Disclosures: **R.R. Riso:** None. **M.J. Carty:** None. **S.G. talbot:** None. **H.M. Herr:** None.

Poster

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Topic: D.18. Brain-Machine Interface

Support: EU FP7 project TOBI 224631

EU H2020 project MoreGrasp H2020-ICT-2014-1 643955

Title: Non-invasive BMI and Neuroprosthesis in spinal cord injury

Authors: R. RUPP[1], *G. R. MUELLER-PUTZ[2];
[1]Univ. of Heidelberg, Heidelberg, Germany; [2]Graz Univ. of Technol., Graz Univ. of Technol., Graz, Austria

Abstract: For individuals with high spinal cord injury (SCI), restoring missing grasping function is a high priority. Neuroprostheses based on functional electrical stimulation (FES) can partly compensate the loss of upper extremity function in people suffering from tetraplegia. With non-invasive, multichannel neuroprostheses a pinch and power grasp can be accomplished for everyday use [Rupp et al. 2012]. Hybrid systems combining FES with active orthoses hold promise for restoring a completely lost arm function. Novel control interfaces are needed to

make full use of the many degrees of freedom of complex hybrid neuroprostheses. Non-invasive electroencephalogram (EEG)-based brain-computer interfaces (BCIs) [Millán et al. 2011] are an emerging technology that may serve as a valuable adjunct to traditional control interfaces for neuro-prosthetic control. Shared control and context-specific autonomy are most effective for reducing the users' workload. The modularity of upper extremity neuroprostheses as well as their associated control interfaces enable customization of the systems to adapt to the impairment and needs of each individual end user. This work provides an overview of the application of noninvasive hybrid BCI [Müller-Putz et al. 2015]-controlled upper extremity neuroprostheses in individuals with high SCI [Rupp et al. 2015]. We start with single use cases on basic hand function control with non-invasive and invasive neuroprosthesis. We continue with the use of an non-invasive hybrid BCI for the control of hand and elbow function and further with the continuous control of an elbow/hand neuroprosthesis in spinal cord injury. These are results from the European Integrated Project Tools for Brain-Computer Interaction. Additionally, we also present latest results from non-invasive movement trajectory decoding [Ofner et al. 2012, Ofner et al. 2014]. Further on, we will describe the challenges and promises for the future, which will be partly covered by the European Horizon 2020 project MoreGrasp.

Disclosures: R. Rupp: None. **G.R. Mueller-Putz:** None.

Poster

612. Brain-Machine Interface Grasping Devices

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Program#/Poster#: 612.06/R1

Topic: D.18. Brain-Machine Interface

Title: Wavelet analysis on electroencephalographic time series to identify key patterns corresponding to arm movements

Authors: *L. GOODMAN, B. DE CELIS ALONSO, E. MORENO BARBOSA;
Facultad de Ciencias Físico Matemáticas, Benemérita Univ. Autónoma De Puebla, Puebla, Mexico

Abstract: Electroencephalography (EEG) is the recording of electric fields produced by neuronal activity within the cerebral cortex by placing electrodes on specific locations of the scalp and measuring evoked potentials. The signals captured by EEG, commonly known as brainwaves, are time series of voltages in the range of 0.1-200 μV. Traditionally, band-pass filters are applied to these signals to break them into δ, θ, α, β and γ frequency bands, each of which has been found to be associated with specific brain activities. *We hypothesize that for each*

of the arm movements performed during our experiment, certain identifying patterns can be found in the corresponding brainwaves which are consistent among all individuals. In our research, twenty right handed male and female subjects perform real and imaginary movements of their right arm as EEG signals are recorded. Our experiment consists of twelve 30-second tests, each composed of 5 repetitions of two opposite movements. Indications on timing, speed, and type of movement are provided by a computer program during the experiment. The 12 tests include two base lines with open and closed eyes, four tests covering all degrees of freedom of the shoulder and elbow, and one for hand movement, as well as imagination of all five movements. We use the Continuous Wavelet Transform to identify how characteristic frequencies change over time, and Wavelet Coherence to determine (a) connections between different brain regions and (b) the degree of similarity between signals from different subjects or tests. We introduce a novel pre-processing technique for phase-independent multiscale addition and subtraction of signals. Preliminary results comparing a single electrode of two subjects performing horizontal arm movement indicate wavelet coherence in the gamma-beta range. Similar studies suggest that motor activity can be deciphered from brainwaves, but to the best of our knowledge, it has yet to be accomplished with a high rate of success. The information obtained in this study regarding the frequencies and brain regions involved in each movement has applications in non-invasive Brain-Computer Interfaces for natural movement of prosthetic or virtual limbs.

Disclosures: L. Goodman: None. **B. de Celis Alonso:** None. **E. Moreno Barbosa:** None.

Poster

612. Brain-Machine Interface Grasping Devices

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Topic: D.18. Brain-Machine Interface

Support: NIH R01 NS053603

Title: Adaptive decoder training for FES neuroprosthesis

Authors: *C. ETHIER[1], D. ACUNA[2], S. SOLLA[1], K. KORDING[2], L. MILLER[1];
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Abstract: Brain-machine interfaces (BMIs) can be used to restore voluntary grasp function after paralysis, through the control of functional electrical stimulation (FES). We have used neuron-to-EMG decoders in the past, to generate muscle activity (EMG) predictions for use as FES control

signals. This approach has the potential to control a large number of degrees-of-freedom, and the flexibility for the user to compensate voluntarily, for external load and muscle fatigue. However, training EMG decoders in paralyzed individuals is challenging because no output signal is available for direct decoder calculation. Kinematic decoders have been trained using observed cursor or robot arm movements, but there is no corresponding way to use a high-dimensional target EMG signal. However, we can estimate the EMG patterns required to produce a given force under simple isometric conditions. Here we present a method that we developed in monkeys, which allows us to compute the relationship between intracortical activity and intended EMG adaptively, without using any recordings of motor output. We trained monkeys at a 2D isometric wrist force task, in which they controlled a computer cursor by applying wrist force in the flexion, extension, ulnar and radial directions. Each trial required the monkeys to move to and hold briefly in a central (zero force) target, followed by one of eight outer targets to obtain a juice reward. We used a muscle-to-force model to relate each target to a muscle activity pattern, by identifying the optimal muscle combination minimizing overall activity. The model was based on generic muscle pulling directions obtained from a stimulation study in humans. We then trained EMG decoders during the target hold periods, with a gradient descent algorithm that compared the EMG predictions to the optimal EMG patterns. We tested this method both offline and online, by feeding the EMG predictions to the generic muscle-to-force model, and quantifying the resulting force prediction accuracy. Our results suggest that this adaptive approach can be used to train neuron-to-EMG decoders suitable for FES control, at least within the constrained biomechanical paradigm of this wrist force task. We plan further developments involving a muscle-to-force model obtained from stimulation that also includes temporal dynamics. We also intend to include multiple grasping tasks, each with it's own muscle-to-force model, to expose the neuron-to-EMG decoder training process to a wider repertoire of actions. We believe that these improvements could lead to EMG decoders that are accurate across tasks, and trainable in paralyzed patients.

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Poster

612. Brain-Machine Interface Grasping Devices

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Topic: D.18. Brain-Machine Interface

Support: MEXT SRPBS

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MHLW HLSRG 23100101

KAKEN 26282165

Title: Severely affected ALS patients have broad and high expectations for brain-machine interfaces

Authors: *M. HIRATA[1], Y. KAGEYAMA[1], T. SHIMOKAWA[2], J. SAWADA[3,4], T. YANAGISAWA[1], M. SHAYNE[1], N. MIZUSHIMA[5], O. SAKURA[5], T. YOSHIMINE[1]; [1]Osaka Univ. Med. Sch., Suita, Japan; [2]Yamanashi Univ., Yamanashi, Japan; [3]Osaka Gen. Med. Ctr., Osaka, Japan; [4]Osaka Intractable Dis. Med. Information Ctr., Osaka, Japan; [5]The Univ. of Tokyo, Tokyo, Japan

Abstract: Objective: Brain-machine interfaces (BMIs) may provide new communication channels and motor function to individuals with severe neurodegenerative diseases, but little is known about their interests in such devices. We investigated the interests of severely affected ALS patients in BMIs, and examined factors that might influence these interests. Methods: We conducted an anonymous, mail-back questionnaire survey of severely disabled ALS patients diagnosed using the revised El Escorial criteria. Results: Thirty-seven patients responded to the questionnaire. Twenty-nine patients (78.4%) had undergone tracheostomy positive pressure ventilation. More than 80% of the patients were interested in communication support. Thirty-three patients (89.2%) felt stressed during communication. Among those using assistive communication devices (17 patients), 15 (88.2%) were not satisfied with these devices. More than 50% of the patients expressed an interest in BMIs. Their expectations of BMIs ranged widely from emergency alarm to postural change. The frequent use of personal computers tended to be correlated with an interest in invasive BMIs ($p = 0.07$). Conclusions: This is the first questionnaire survey demonstrating that severely affected ALS patients have broad and high expectations for BMIs. Communication was the most desired support from BMIs for such patients. We need to meet their widely ranging expectations of BMIs.

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Poster

612. Brain-Machine Interface Grasping Devices

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Title: Decoding of limbs movement from magnetoencephalography for BCI applications

Authors: *T. AKSENOVA[1], M.-C. SCHAEFFER[1], V. ROHU[1], N. TARRIN[1], E. LABYT[1], I. VERGARA[1], B. MORINIERE[2], A. ELISEYEV[1], C. MESTAIS[1], A.-L. BENABID[1]; [1]CLINATEC, CEA-LETI MINATEC, Grenoble, France; [2]CLINATEC, CEA-LIST, Grenoble, France

Abstract: Chronic clinical Brain Computer Interface (BCI) is the challenge of BCI project at CLINATEC®/LETI/CEA. The goal of the project is to improve tetraplegic subjects' quality of life by allowing them to interact with their environment through the control of effectors with multiple degrees of freedom after training. The project includes the chronic wireless ECoG recording implant WIMAGINE®, a 4-limb exoskeleton EMY, a software platform and signal decoding algorithms. A pre-clinical study yielded satisfying movement reconstructions from neural activity on ECoG non-human primate data. To prepare BCI clinical application, preliminary studies on human data were carried out using non-invasive MagnetoEncephaloGraphy (MEG). Clinical trials have been agreed by Ethical Committee and ANSM. The brain activity of control subjects was recorded by a MEG acquisition system while they were executing real or imagined limbs movements: (A) 3D hand trajectory reconstruction was studied on 5 control subjects. Two 4-min sessions were performed for the paradigms: cue-paced execution of stereotypical movements (1), self-paced execution of stereotypical movements (2), execution of self-paced free hand movements (3). Predefined stereotypical movements consisted in rectilinear trajectories of the hand from an idle position along the axis x, y, z. Execution of movements was randomized in time. Hand coordinates were tracked using a MEG compatible tracking system. (B) Imagination of stereotypical movements (see A) was performed by 2 subjects in different paradigms. (C) Preliminary study of real alternative multi-limbs 1D trajectory decoding was performed in 1 control subjects (2 hands, 2 hands+1 leg correspondingly). In all the cases, 36 sensors (12 magnetometers and 24 gradiometers) facing the subject's sensorimotor area were selected by an expert for the decoding purpose. Time-frequency

features were extracted using continuous wavelet transforms. A decoding model was identified using Partial Least Squares combined with Generalized Linear Model [1]. 8-fold cross-validation was performed to assess the accuracy. Preliminary results for 3D hand trajectory reconstruction (A) yield Pearson Correlation Coefficient (PCC) in the range of 0.2 to 0.7, depending on paradigm (1-3) and axis (average PCC = 0.42±0.11 for 3 coordinates, 3 paradigms, 2 sessions per paradigm, 5 subjects). An average PCC = 0.31±0.13 was found for 3D cued-paced imagined movements (B) (3 coordinates, 2 sessions, 2 subjects). PCCright hand = 0.55, PCCleft hand = 0.42 and PCCfoot = 0.26 were found for multi-limb movement (C) (2 sessions, 1 subject).
1.Eliseyev, A., & Aksenova, T. J. Neural Eng., 2014, 11(6), 066005.

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Poster

612. Brain-Machine Interface Grasping Devices

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Topic: D.18. Brain-Machine Interface

Title: Real-time myoelectric control of a virtual upper limb prosthesis via lower leg gestures: Preliminary results

Authors: *K. R. LYONS, S. S. JOSHI;
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Abstract: Few options are currently available for high-level upper limb amputees to control a powered prosthetic arm. Existing techniques are either invasive, requiring surgery and recovery time (approximately one year), or are complex, requiring significant training time (several weeks). We have developed a noninvasive technique where lower leg and foot gestures recognized by surface electromyography (EMG) map to homologous movements of the prosthetic arm and hand. The mapping is based on the alignment of the degrees of freedom of the wrist and ankle in addition to the similarity of finger and toe movements (grasps), so each of the mapped gestures are intuitive and the entire mapping takes less than five minutes to learn. Our previous work has demonstrated that 10 or more lower leg and foot gestures can be recognized offline via surface EMG, and we now present the results of a real-time experiment in which subjects controlled a simulated prosthetic arm using this technique. The Target Achievement Control (TAC) test was used as an experimental task to evaluate subjects' ability to move the

virtual arm to target postures offset from the neutral posture in several degrees of freedom. Common performance metrics for this task are presented and compared to the case in which subjects used arm gestures, recorded via an analogous surface EMG configuration on the arm, to perform the same task.

Disclosures: **K.R. Lyons:** None. **S.S. Joshi:** None.

Poster

612. Brain-Machine Interface Grasping Devices

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Title: Contralateral and ipsilateral gesture decoding in epilepsy patient using electrocorticographic signals

Authors: *Y. JIN[1,2], X. WANG[1], M. LU[1,2], S. ZHANG[1,2], J. ZHU[1,3], X. ZHENG[1,2]; [1]Qiushi Acad. For Advanced Studies, Zhejiang Univ., Zhejiang, China; [2]Dept. of Biomed. Engin. and Instrument Science, Zhejiang Univ., Zhejiang, China; [3]The Second Affiliated hospital of Zhejiang Univ. Sch. of Med., Zhejiang, China

Abstract: Ipsilateral decoding is a hot topic in Brain-machine interface (BMI) nowadays, which can extend the application of BMI to help the patient whose contralateral brain was injured to restore their motor function. Electrocorticography (ECoG) signals are proved available signal source in BMI with high spatial resolutions. In our study, two participants undergoing invasive electrocorticographic monitoring for seizure localization were asked to perform three types of

gestures following visual cues. The two participators completed the task with their left hand and right hand respectively. Subdural electrodes were placed over their sensorimotor cortex to collect the ECoG signals. Power spectrum of high gamma frequency components (80-120Hz) of ECoG signals was extracted to decode their hand gestures. The best accuracy of contralateral decoding and ipsilateral decoding were 60% and 64% for participator 1 and 64% and 68% for participator 2. There was no significant difference between the performance of contralateral decoding and ipsilateral decoding ($p>0.05$, $p=0.50$ for participator 1 and $p=0.76$ for participator 2). Our result exhibited that ipsilateral decoding using electrocorticographic signals was available, whose performance was not worse than the contralateral one.

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Poster

612. Brain-Machine Interface Grasping Devices

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Title: Real-time decoding of individual and combined finger movements from macaque area AIP, F5, and M1

Authors: ***W.-A. SHENG**, A. AGUDELO-TORO, H. SCHERBERGER;
Neurobio., German Primate Ctr., Goettingen, Germany

Abstract: Recent neuro-prosthetic studies have allowed patients to control artificial arms and hands, but these devices have been largely restricted to reaching and simple hand closure commands. Offline studies have demonstrated high accuracy decoding of individual and combined finger movements but real-time decoding studies have been restricted to grip types or individual finger movements. We report the decoding of individual and combined finger movements online from three areas in macaque cortex reaching up to 91% accuracy. A macaque monkey was trained in a delayed finger task with visual cues, in which the thumb (f1), index (f2) and middle (f3) finger were flexed and hold individually or in combination with neighboring fingers (5 conditions). A micro-switch manipulandum detected flexion movements and provided tactile feedback. The task consisted of several epochs, in which “fixation”, “cue”, “go”, and “hold” were used for decoding. We acquired single-unit activity simultaneously from the left

anterior intra-parietal area (AIP), area F5 of the ventral premotor cortex, and the hand area of primary motor cortex (M1) using two 32-channel floating microelectrode arrays for each area (total 192 channels). Spikes were sorted online, counted in 40ms bins, and fed in real-time to a Naïve Bayesian classifier. Over 8 days, 17 decoding runs were performed. In each, the decoder was trained online with ~10 correct trials per condition before real-time decoding. Finger classification performance over 17 runs ranged from 68% to 91% (mean 80%) for the hold epoch using all areas (fixation: 21%, cue: 52%, go: 66%; chance level 20%). During the hold epoch, movements were best decoded using all areas combined (M1 75%, F5 59%, AIP 47%) but M1 alone was not significantly worse (ANOVA, $p<0.05$). Among the five single and combined finger movements, f1 could be best decoded (86%), followed by f3 (85%) and f2 (78%), while decoding of f2+f3 performed least (72%). The important combination f1+f2 was correctly decoded 78% of the time. On average, 154 online spike-sorted units (M1 61, F5 62, AIP 30) were used for decoding, from which 56% of the M1 units were tuned to the task (F5 49%, AIP 30%, ANOVA, $p<0.05$). Previous offline studies demonstrated that, in contrast to individual fingers, it is intrinsically hard to decode combined finger movements due to the non-linearity of the neuronal response. Here, we decoded individual and combined finger flexion simultaneously from M1, F5, and, AIP in contrast to previous studies that were limited to individual movements and to M1. We could determine possible cortical area combinations for decoding, which may be useful for future neuro-prosthetic device developments.

Disclosures: W. Sheng: None. **A. Agudelo-Toro:** None. **H. Scherberger:** None.

Poster

612. Brain-Machine Interface Grasping Devices

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 612.13/R8

Topic: D.18. Brain-Machine Interface

Support: NIH R21 HD081938

The Grainger Foundation

Title: Functional testing of a soft-synergy based artificial prosthetic hand

Authors: *A. GAILEY[1], S. GODFREY[2], R. BREIGHNER[3], K. ANDREWS[3], K. ZHAO[3], A. BICCHI[2,4], M. SANTELLO[1];
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Abstract: The loss of a hand can dramatically affect the ability to perform activities of daily living, and thus quality of life. Although many commercially-available prosthetic hands exist, rejection rates remain high in part due to their limited function. To address these limitations, the University of Pisa and the Italian Institute of Technology have created a myoelectric artificial hand, the SoftHand, whose design combines soft robotics and the concept of hand synergies. The hand consists of 19 joints. Motion occurs along the 1st principal component of kinematic hand synergies and is generated by a single motor. The user controls the SH via electromyographic (EMG) signals from two antagonistic wrist muscles. The present study was designed to quantify grasp performance of the SH in able-bodied subjects. We asked subjects (n = 19) to grasp and lift an object while recording forces on the object, object kinematics, and EMG signals. We measured the contact-to-lift time, hold, and object placement (total task duration), changes in total grip force as a function of practice, and native hand performance (20 trials). SoftHand trials were performed at two different weights (667 g and 1067 g) 30 trials each to assess grip force modulation in response to object weight. We also assessed effects_on grasp performance_of training exercises consisting of tracking a cursor on a computer monitor by opening and closing the SH. Subjects were randomly divided into four experimental groups, with each given a 10-15 minute familiarization period with the SH plus the experimental training and then tested on the grasp-and-lift task the next day. Group 1 underwent training as described above; Group 2 had 45 minutes of exploratory practice; Group 3 received half-doses of both training and exploratory practice; and Group 4 had no training beyond the familiarization period. The type of practice did not systematically affect our behavioral measures. After pooling data across all groups we found that, even though total task duration was longer when using the SH vs. the native hand (mean across all trials ±S.E.: 7.06 ±1.25 s and 2.17 ±0.1), subjects' performance with the SH improved with practice. Specifically, average total task duration decreased from 10.13 ±1.91 s on the first 10 trials to 5.94 ±0.88 s on the last 10 trials. Greater object weight caused a larger grip force in both native hand and SH; the difference was larger for the native hand (~5.5 N vs. ~1.5 N, respectively). Although preliminary, these data suggest that the SH has promising potential for prosthetic use. Current work is examining design modifications to improve the function of the SH. Grant support: NIH R21 HD081938 and The Grainger Foundation.

Disclosures: **A. Gailey:** None. **S. Godfrey:** None. **R. Breighner:** None. **K. Andrews:** None. **K. Zhao:** None. **A. Bicchi:** None. **M. Santello:** None.

Poster

612. Brain-Machine Interface Grasping Devices

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Program#/Poster#: 612.14/R9

Topic: D.18. Brain-Machine Interface

Support: Wallace H. Coulter Foundation

Craig H. Neilsen Foundation

Title: Peripheral and cortical decoding of individuated finger movement in the rhesus macaque

Authors: ***Z. T. IRWIN**[1], P. P. VU[1], A. J. BULLARD[1], I. C. SANDO[2], J. N. BENTLEY[3], M. G. URBANCHEK[2], P. G. PATIL[3,1], P. S. CEDERNA[2,1], C. A. CHESTEK[1];
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Abstract: Brain-machine interfaces (BMIs) are a promising technology for enabling the effective control of advanced prosthetic limbs. However, the ability of BMIs to reproduce hand-level fine motor skills is still relatively lacking. Here, we investigate the feasibility of extracting finger-level motor information from both cortical and peripheral neural sources. We trained two rhesus macaques to perform index finger movements to acquire virtual targets on a monitor, recording finger position via a flex sensor on the index finger. In one monkey, we implanted two intracortical electrode arrays in M1, one 96-channel Utah array (Blackrock Microsystems) and one 16-channel FMA (Microprobes). In a second monkey, we recorded signals from the median and radial nerves in the forearm via three Regenerative Peripheral Nerve Interfaces (RPNIs). The RPNI is a novel interface consisting of a free muscle graft implanted on the end of a transected nerve fascicle. After implantation, the nerve fascicle re-innervates the graft, which then acts as a bioamplifier for the efferent signals. To record these signals, we implanted one bipolar intramuscular EMG electrode (Ardiem Medical) in each RPNI. We performed two decodes for each signal modality, using neural spikes (thresholded at -4.5*RMS) as the cortical data feature and waveform signal power and line length as the EMG features. First, we predicted continuous 1D finger position and velocity (as a percent of flexion) via a linear Kalman filter, using 100ms bins and including 5 bins of neural history for the cortical decode. Second, we used linear discriminant analysis to classify movement type (flexion vs. extension vs. rest) for a variably-sized window centered on the manually-labeled movement onset. For the continuous cortical decode using 10-fold cross-validation, the predicted and true finger positions had a correlation coefficient (ρ) of 0.88, and a root mean squared error (RMSE) of 0.12 (an average error of ~12% of the full range of movement). For the continuous EMG decode using 10-fold cross-validation, $\rho = 0.82$ and RMSE = 0.13. For the discrete classifications, we lowered the window size to 50ms for EMG and 200ms for cortical without losing significant performance. Using leave-one-out cross-validation, the EMG decode was 97.7% correct and the cortical decode was 95.3% correct (out of 261 and 342 movements, respectively, with chance at ~33%). These results demonstrate that accurate finger kinematics can be extracted from both cortical and peripheral sources. It remains to be seen whether the presented decodes can be used effectively in a closed-loop setting. This could, in the future, allow BMIs to reproduce dexterous hand movements.

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Poster

612. Brain-Machine Interface Grasping Devices

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Topic: D.18. Brain-Machine Interface

Support: NSF-NRI 1317379

NIH NRSA F31 HD080335-01A1

Title: Measuring the influence of EMG control on feedforward uncertainty

Authors: ***R. JOHNSON**[1,2], K. KORDING[1,2], L. HARGROVE[1,2], J. SENSINGER[3,2]; [1]Rehabil. Inst. of Chicago, Chicago, IL; [2]Northwestern Univ., Chicago, IL; [3]Univ. of New Brunswick, Fredericton, NB, Canada

Abstract: Movements with powered upper limb prostheses are currently imprecise and unpredictable, which degrades the ability to perform everyday tasks. The movement unpredictability, or feedforward uncertainty, may be caused in a large part by the use of EMG control, which is highly variable and is shown to increase errors relative to able-bodied joint angle or torque control. To reduce movement uncertainty, we first need to understand the sources of uncertainty during prosthesis control. However, uncertainty is typically inferred through observing behavior, or assumed to be represented by variability or error. In this experiment we dissociate error and uncertainty by explicitly quantifying feedforward uncertainty. We compare feedforward uncertainty during the use of EMG control, torque control, and torque control with added noise. The torque+noise condition was meant to create a wider range of movement performance, which allowed us to analyze uncertainty as a function of mean absolute error. Feedforward uncertainty was quantified by measuring the just noticeable difference of a visual perturbation. We found that for equal errors, EMG resulted in higher feedforward uncertainty than both torque and torque + noise.

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Poster

612. Brain-Machine Interface Grasping Devices

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Topic: D.18. Brain-Machine Interface

Support: DARPA RNR subcontract for project W31P4Q-12-C-0200

Title: EEG-controlled functional electrical stimulation of paralyzed hand muscles in subjects with chronic, complete, cervical spinal cord injury for grasp and release

Authors: *K. GANT, L. ZIMMERMAN, Z. XIE, J. C. SANCHEZ, A. PRASAD;
The Univ. of Miami, Miami, FL

Abstract: Over 33,000 people in the United States are living with complete tetraplegia caused by cervical spinal cord injury (SCI), which results in paralysis of hand muscles. This population relies heavily on caregivers and family, due to an inability to perform activities of daily living. In these individuals, the options for hand function rehabilitation are limited since improvements are not expected during the chronic phase. People with complete tetraplegia rank restoration of arm and hand function as most important to them, as it would increase independence and improve their quality of life. In this study, we show that subjects with chronic C5/C6-level, motor-complete SCI are able to control a brain computer interface-functional electrical stimulation (BCI-FES) system to perform a grasp and release task. The subjects (SCI and uninjured controls) participated in 6 days of BCI-FES training over a period of 3 weeks, consisting of 120 closed-loop trials each day. Visual cues were presented to the subject on a computer screen, instructing them to either relax or imagine movement of their right hand. Electroencephalographic (EEG) signals were acquired using a wireless 20-channel EEG system at 256 Hz sampling rate and 16-bits resolution (X24 headset, Advanced Brain Monitoring, Carlsbad, CA). We extracted average power in 5 Hz bins (6-35 Hz) from C3, C1, Cz, C2, and C4 electrodes and input as features to a Support Vector Machine (SVM) classification algorithm. When “movement” was classified correctly from the EEG motor imagery, a custom-designed stimulation sequence was delivered to the forearm muscles (extensor digitorum profundus, extensor digitorum superficialis, and extensor pollicis longus, flexor digitorum superficialis, flexor digitorum profundus, 200 μs pulse width, 35 Hz) to enable opening and closing of the hand for grasp and release. Although classification accuracies started off low during the first day of training (49% for control, 52% for SCI), they improved over the training period. By day 6, overall accuracy for the control subject averaged 73% (± 2.2%), while the SCI subject achieved 80% (± 1.8%) accuracy. This study shows that subjects with motor complete, cervical SCI were able to control a BCI-FES system after a brief training period. BCI-FES systems may have the potential to restore hand function in

people with motor-complete SCI, which would increase independence and improve quality of life.

Disclosures: **K. Gant:** None. **L. Zimmerman:** None. **Z. Xie:** None. **J.C. Sanchez:** None. **A. Prasad:** None.

Poster

612. Brain-Machine Interface Grasping Devices

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Topic: D.18. Brain-Machine Interface

Support: EU AIDE 645322

EU WAY 288551

BMBF 01GQ0831

BMBF 16SV5838K

DFG SO932-2

Title: Restoration of hand function in daily life using a brain/neural interface controlled hand-exoskeleton

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Abstract: Background: High-level spinal cord injuries (SPI) are often associated with complete loss of hand function. While the majority of individuals with SPI have sufficient shoulder and arm function to perform reaching movements, severe or complete finger paralysis incapacitates them to grasp, hold or manipulate daily life objects. Here we tested whether a non-invasive autonomous brain/neural-computer interaction (BNCI) system that translates neuronal activity and eye movements into grasping motions of a hand-exoskeleton can restore hand function to grasp and manipulate daily life objects. Method: Two individuals (one male, 26.0±8.48 years)

with complete (Asia Impairment Scale A) and incomplete (Asia Impairment Scale B) chronic SPI and severe loss of hand function participated in the study. All participants performed the Toronto Rehabilitation Institute Hand Function Test (TRI-HFT) to assess their ability to grasp and manipulate daily life objects without (baseline) and with the BNCI system. Results: After calibration and familiarization, participants were able to control the BNCI hand-exoskeleton system. TRI-HFT scores increased from 42.75±25.1 at baseline to 109.5±16.26 (max. score: 133) under BNCI hand-exoskeleton control documenting hand function close to normal. Conclusion: Non-invasive brain/neural hand-exoskeleton systems are powerful tools to restore autonomy and independence of individuals with high-level SPI. Integration of such systems and fusion with other assistive tools may significantly improve paralyzed individual's quality of life and accessibility.

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Poster

612. Brain-Machine Interface Grasping Devices

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Topic: D.18. Brain-Machine Interface

Support: NIH R01 NS-063372

Title: Changes in LFP power during motor learning in brain-machine interface

Authors: R. JIE CUI, M. ARMENTA SALAS, *S. I. HELMS TILLERY;
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Abstract: The study of the neural correlates of motor learning is a primary focus of neuroscience. Previous studies have shown that local field potentials (LFPs) measured at the motor and premotor cortices can encode a variety of parameters, from behavioral states to motor execution. However, quantitative information about LFPs and motor learning is lacking. Here we study the changes of the band-limited power (BLP) of LFPs recorded in motor cortical areas while a monkey learned to control a computer cursor in a 3D center-out task via brain-machine interface. In this task, the control of the cursor was initially learned using a population vector algorithm. The animal was then challenged by introducing perturbations in the control mapping between neural signals and movement. We changed the control algorithm either by using a visuomotor rotation or by using a decorrelation approach, in which pairs of neurons that were

normally highly correlated were required to be uncorrelated in the control algorithm. We found that, in general, the power of beta-band (15-30 Hz) activity was significantly elevated during the sessions of perturbation. Moreover, the spectra of LFPs indicate differences between the two types of perturbation. Finally, our preliminary results suggest a linear correlation between BLP of very low frequency bands (1-8 Hz) and success rate of trials, implying a potential role of LFP in motor learning

Disclosures: **R. Jie Cui:** None. **M. Armenta Salas:** None. **S.I. Helms Tillery:** None.

Poster

612. Brain-Machine Interface Grasping Devices

Location: Hall A

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Program#/Poster#: 612.19/R14

Topic: D.18. Brain-Machine Interface

Title: Radio-transparent enclosures for enabling wireless home-cage recordings of non-human primates

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Abstract: Studies of the non-human primate (NHP) motor system generally involve a head-fixed animal performing a limited set of learned motions. Such motions represent only a subset of the complex movement repertoire. Recently, a wireless neurosensor capable of recording neural activity during unconstrained movements has become commercially available. With the introduction of this small, lightweight, wireless neural recording technology, experiments no longer require animals to be head-fixed or otherwise restrained during recordings. For example, long-term recordings in the animal's home-cage become possible, enabling scientific exploration of social behavior, adaptation, and learning. Current wireless solutions use radio frequency (RF) far-field transmission to stream data. Traditional metal cages block this signal from leaving the enclosure's boundary. To address this issue, we developed a non-metallic, dielectric cage that is transparent to RF radiation. We show that broadband neural data can be wirelessly transmitted and recorded from a naturally behaving animal to external receiving equipment for further processing and interpretation. Using a neural signal simulator, the cage was validated to ensure that data could be successfully retrieved from inside the enclosure. Components constructed from a thermoplastic laminate, as well as polycarbonate and a fiberglass, thermoset polyester

composite, were used as strong, non-conductive alternatives to steel preventing absorption or scattering of the radio signals. The final construct contains less than 5% electrically conductive components. The transparent home-cage system is not limited to studies of the motor system. As animals perform daily tasks in their home environment, neural systems can be interrogated with contextual relevance, for instance during sleep. Complex social interactions can be studied, as animals may be left undisturbed to socialize with their peers while researchers observe remotely. As new neural recording technologies are developed, they can be seamlessly integrated into the new housing system. Using this tool, neural signal collection can now be performed throughout an animal's daily routine enabling researchers to ask new and interesting questions about the nervous system.

Disclosures: **M. Powell:** None. **D. Xing:** None. **R. Darie:** None. **A. Gregoire:** None. **J.B. Zimmermann:** None. **W. Britz:** A. Employment/Salary (full or part-time):; Britz and Company. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Britz and Company. **J.S. Harper:** None. **D.A. Borton:** None.

Poster

612. Brain-Machine Interface Grasping Devices

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Topic: D.18. Brain-Machine Interface

Support: Memorial Hermann Foundation

Title: Myoelectric pattern recognition control of a wearable exoskeleton hand

Authors: **Z. LU**[1], K.-Y. TONG[2], *P. ZHOU[1];
[1]PM&R, Univ. of Texas Hlth. Sci. Ctr. At Houst, Houston, TX; [2]The Chinese Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: Robot-assisted training is an effective approach to neurologic injury (such as stroke, spinal cord injury or cerebral palsy) rehabilitation. Compared with passive training, the active or voluntary implementation of tasks with the user's intention input can enhance therapeutic effect and promote motor learning as well. Active myoelectric control has been developed for robot-aided therapy, primarily based on an "on-off" or proportional strategy. On the demand for the mobility of assistive devices, a more advanced myoelectric control strategy is required (to overcome the limitation of the one-to-one mapping between a muscle and a degree-of-freedom).

This is particularly important for a hand exoskeleton or robot due to hand dexterity. To meet this need, a myoelectric pattern recognition framework was implemented in this study to control a wearable exoskeleton hand (Hand of Hope, Rehab-Robotics Company Ltd, Hong Kong) in real time. The framework used four channels' surface electromyogram (EMG) acquired from the flexor carpi radialis, flexor carpi ulnaris, extensor digitorum, and abductor pollicis brevis muscles, respectively. A pattern recognition algorithm based on a RMS +WL+AR feature set (i.e. a combination of root mean square amplitude, waveform length, and 4th order auto regressive coefficients) and a Bayes classifier was implemented on 200 ms analysis windows (with 100 ms overlapping). This was used to identify 6 different hand patterns: hand closing and opening (HC & HO), thumb, index and middle finger closing and opening(TIMC & TIMO), middle, ring and little finger closing and opening (MRLC & MRLO). Once a motion intention was detected, the exoskeleton hand performed the motion task. Five neurologically intact subjects (32.0 ± 6.0 years, 1 female, 4 male) participated in the study. For each subject, at least 300 analysis windows were recorded for each hand pattern to train the classifier. Then, performance of the myoelectric pattern recognition control for the exoskeleton hand was tested. Across different hand patterns, the overall control accuracy was 98.4 ± 3.6% with an algorithm delay approximately 38 ms (Intel Core i5 4690S, 8GB RAM). The average completion time for each hand pattern was 6.4 ± 1.7s, including 2.3 ± 1.6 s waiting period. Current experimental results demonstrated the feasibility of applying myoelectric pattern recognition for controlling the exoskeleton hand, which will be further tested with neurological injury patients for hand function restoration.

Disclosures: Z. Lu: None. **K. Tong:** None. **P. Zhou:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 613.01/R16

Topic: E.01. Neuroendocrine Processes

Support: NINDS R01 NS055125

Emory Neuroscience Initiative (Yerkes)

Title: Time course of photoperiodic responses in the hypothalamus of a seasonally breeding songbird

Authors: *S. EDWARDS[1], R. A. ALDREDGE[2], A. M. IANCU[1], N. P. JAMES[1], K. W. SOCKMAN[2,3], D. L. MANEY[1];
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Abstract: Seasonally-breeding birds use day length as an initial predictive cue to time gonadal recrudescence and the onset of reproduction. The neural response to photostimulation culminates in the release of gonadotropin-releasing hormone (GnRH) from the median eminence of the hypothalamus. We previously showed that in white-throated sparrows (Zonotrichia albicollis), a North American seasonal breeder, GnRH neurons in the preoptic area express the immediate early genes Egr-1 and FOS by the morning following the first long day. It remains unclear, however, when during the night the GnRH neurons begin responding to the long day, and whether other neural responses precede or follow GnRH responses. In this study, photosensitive male white-throated sparrows in non-breeding condition were housed on short days (8L:16D), then half were exposed to a single long day (16L:8D). We collected brain tissue at three intervals: 10-14 hours, 18-20 hours, and 24-26 hours after dawn of that long day. Using immunohistochemical labeling, we found that Egr-1 expression was not induced in GnRH neurons until 26 hours after dawn. In contrast, Egr-1 was induced elsewhere in the brain at earlier time points. For example, we noted considerable induction of Egr-1 throughout the mediobasal hypothalamus (MBH), including the lining of the third ventricle, in long-day birds by 18 hours. This response persisted until at least 26 hours. Immunohistochemical co-labeling of tyrosine hydroxylase showed that a subset of the responding cells belonged to dopaminergic cell groups in the ventral and caudal portions of the MBH. These findings led us to do a follow-up study to determine exactly when during the night the Egr-1 response begins. Using tissue collected from males between 13 and 18 hours after dawn on the first long day, we noted Egr-1 induction in the infundibular nucleus of the MBH as early as 15.2 hours after dawn, and in the lining of the third ventricle one hour later. The Egr-1 response in the dopaminergic cells of the MBH increased significantly by 16.5 hours. Egr-1 expression throughout the MBH was robust in all birds by 17 hours after dawn. Our results indicate that compared with neural responses in the MBH, the GnRH cell population responds to photostimulation relatively late in the cascade of events. Induction of immediate early genes in GnRH neurons may reflect new synthesis related to GnRH depletion rather than stimulation by light cues.

Disclosures: S. Edwards: None. **R.A. Aldredge:** None. **A.M. Iancu:** None. **N.P. James:** None. **K.W. Sockman:** None. **D.L. Maney:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 613.02/R17

Topic: E.01. Neuroendocrine Processes

Title: Gonadal regression elicited in Pekin duck drakes and hens associated with a drop in light intensity

Authors: *G. S. FRALEY;
Hope Col., Holland, MI

Abstract: Many studies have focused on the neural mechanisms associated with seasonal reproduction in birds and the light intensity necessary to initiate gonadal recrudescence. However, few studies have examined the drop in light intensity that initiates gonadal regression. The Pekin duck is an excellent model for the study of seasonal reproduction and the question regarding the neurobiology of gonadal regression is important in the US duck poultry industry. To more fully understand the relationship between light intensity and gonadal regression we housed adult (45 week old) drakes and hens were housed in the Hope College aviary as 4 drakes:20 hens in each of 3 floor pens (density = 0.24 m2 per duck). Light conditions were divided into the following: 1) to simulate summer, 14 hrs 75 Lux with 10 hrs 1 lux; 2) to simulate winter, 8 hrs 75 lux with 16 hours 1 lux; 3) winter augmented, 8 hrs 75 lux with 16 hours with 25 lux. Daily, total number of eggs laid and a daily average of eggs laid calculated for each week of the study. Weekly, eggs were weighed and the perivitilline membrane was assayed for number of sperm holes as an indirect measure of drake fertility. As expected, winter conditions caused a significant ($p < 0.01$) reduction in the percent of eggs laid and a significant ($p < 0.001$) reduction in the number of fertilized eggs compared to the summer light conditions. The augmented winter light conditions prevented the loss in the percent eggs laid and fertilized eggs. Surprisingly, even after 5 weeks of the study, the winter conditions did not cause a complete loss of fertility in the Pekin ducks. Although a minimum (1 lux) of light is capable of maintaining some fertility, commercial Pekin duck barns might want to increase the augmented light to 25 lux in order to maintain fertility during winter months. Furthermore, it appears that the drakes may be more sensitive to environmental light conditions than are hens.

Disclosures: G.S. Fraley: None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: E.01. Neuroendocrine Processes

Title: Increased hypothalamic GnIH-ir and decreased reproductive behaviors in an inbred line of Single Comb White Leghorn egg-layers, GHs6

Authors: *H. M. POTTER[1], E. ALENCIKS[2], L. PORTER[2], M. SHANNON[2], G. S. FRALEY[2]; [2]Biol., [1]Hope Col., Holland, MI

Abstract: An inbred line of White Leghorn chickens has been housed at the University of Wisconsin for decades. This line of birds could only be propagated by artificial insemination despite that researchers in the past demonstrated that the hens laid eggs at a typical leghorn rate, and the roosters produced good quality semen, though of slightly, but significantly lower sperm count compared to controls. Thus we hypothesized that the lack of fertility in these birds was due to deficits in reproductive behaviors. To test this hypothesis, a remote surveillance system was was set up over the floor pens (n = 3) that contained roosters and hens (1:4 ratio) housed on 18 hrs of daylight. Constant remote monitoring continued for 6 months, and reproductive and aggressive behaviors were assayed once per week for 3 hours after lights-on. Controls were standard white leghorns (SWLR) housed in a similar fashion with remote surveillance in the Hope College aviary (n = 3 pens). We focused on the roosters' behaviors and found no differences in thrusts or pecks between the inbred and standard leghorns. However, unlike the SWLR the GHs6 roosters showed zero courtship or mating behaviors. Gonadotropin inhibitory hormone has been described in birds to stimulate food intake, and to inhibit both the HPG axis and reproductive behaviors. Thus we hypothesized that the lack of reproductive behaviors in GHs6 roosters may be due to an overexpression of GnIH. To test this hypothesis, 45 week old GHs6 and SWLR (n = 4 per strain) roosters were euthanized and pericardially transfused with 4% paraformaldehyde. Brains were processed for immunocytochemical analyses of GnIH-immunoreactivity (ir). A significant ($p < 0.05$) increase in the number of GnIH-ir perikarya were observed in the paraventricular nucleus of the hypothalamus in GHs6 roosters compared to SWLR controls. The increased GnIH protein expression may be related to the loss of reproductive behaviors in the Single comb white Leghorn roosters.

Disclosures: H.M. Potter: None. **E. Alenciks:** None. **L. Porter:** None. **M. Shannon:** None. **G.S. Fraley:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 613.04/R19

Topic: E.01. Neuroendocrine Processes

Title: Lack of effects on growth and body weight gain after elimination of the leptin receptor from the brain of immature Pekin drakes

Authors: *L. M. PORTER, E. ALENCIKS, K. FRAZIER, A. PORTER, G. S. FRALEY; Biol., Hope Col., Holland, MI

Abstract: The presence of the hormone leptin (LEP) is a controversial topic in the field of avian physiology. While LEP is well understood in mammals, the hormone has not been definitively verified in avian species. Although the hormone remains elusive, the leptin receptor (LEPR) has been identified and sequenced in multiple avian species. Its role, however, remains unclear. To attempt to deduce the role of the leptin system in birds, we focused on altering the leptin receptor expression in the brain of immature Pekin ducks. We hypothesized that eliminating the LEPR-expressing neurons of the hypothalamus would elicit an increase in body weight, as is the case for mammals. To test this hypothesis, we injected stereotaxically 3 µl of a solution containing a monoclonal antibody (anti-LEPR) conjugated to saporin (LSAP, 100 ng/µl) was injected into the lateral ventricle of 10 day old Pekin ducks (LSAP, N = 10). Control group animals (SAP) were injected with unconjugated antibody and saporin at equimolar concentrations to the LSAP. Ducks were weighed weekly starting at 3 days of age. After a final weight was obtained at 50 days of age, ducks were euthanized and a blood sample was collected and sent out for an avian panel to assay serum glucose and free fatty acids. We found that the elimination of LEPR had no significant effect on the body weights of the ducks ($p>0.05$). In addition, The CBC panel did not reveal any significant differences in the overall health of the ducks in each treatment group. Our data indicates LEPR may not play a significant role in the regulation of body weight or growth in juvenile ducks.

Disclosures: L.M. Porter: None. **E. Alenciks:** None. **K. Frazier:** None. **A. Porter:** None. **G.S. Fraley:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 613.05/R20

Topic: E.01. Neuroendocrine Processes

Title: Immunolesions of melanopsin receptive neurons attenuates the hormonal reproductive axis in the adult but has no effect on growth in immature Peking ducks

Authors: *E. ALENCIKS[1], K. FRAZIER[2], A. PORTER[2], G. FRALEY[2];
[2]Biol., [1]Hope Col., Holland, MI

Abstract: Several light sensitive receptors have been described in the avian brain that are thought to regulate the reproductive axis independently from the eyes and pineal gland. Recently, our lab has described the presence of 3 photoneuroendocrine systems in the Pekin duck: rhodopsin, opsin 5, & melanopsin. We set out to test the hypothesis that melanopsin receptive neurons are necessary to maintain seasonal reproductive status along with growth and development in the Pekin drake. To accomplish these goals we first investigated 50-week-old Pekin drakes that were housed in the aviary at Hope College under long day length (18 hrs lights on) conditions in floor pens. To specifically lesion melanopsin-receptive neurons, 3 µl of an anti-melanopsin-saporin conjugate (MSAP, 100 ng/ul) was injected into the lateral ventricle (n = 10). Control drakes were injected with 3 ul of equimolar unconjugated anti-melanopsin and saporin (SAP, n = 10). The drakes were returned to the aviary after complete recovery. Reproductive behaviors were analyzed weekly in a test pen with adult hens. After 4 weeks, birds were euthanized and body weights were measured, and brains, pituitaries, and testes collected and stored for analyses. To test melanopsin's effect on immature ducks the same surgery was performed on a group of 10 day old ducks (n= 10). Ducks were weighed weekly starting at 3 days of age. After a final weight was obtained at 50 days of age, ducks were euthanized and a blood sample was collected and sent out for an avian panel. Mature MSAP-treated drakes had significantly ($p< 0.001$) reduced relative teste weights compared to SAP controls. qRT-PCR analyses (n= 3 per treatment) of anterior pituitary showed a significant reduction ($p< 0.001$) in both LH-beta and FSH mRNA's. Immunoctyochemical analyses (n= 3 per treatment) showed a significant reduction in melanopsin and GnRH-immunoreactivities. Immature drake BW did not differ significantly between MSAP and SAP animals at any of the measured days. The data appeared to drift toward significance near the end of the sampling period ($p = 0.297$). Blood panel results revealed no significant differences between MSAP and SAP animals in any CBC component. Serum glutamic-oxaloacetic transaminase (SGOT) ($p= 0.022$) and creatine phosphokinase (CPK) values were significantly elevated ($p = 0.006$) in MSAP animals compared to controls. Although melanopsin neurons in the PMM appear to have an important role in adult drakes, their importance in the growth of immature ducks is still unclear. However, these data underscore the importance of the photoneuroendocrine system in maintaining the reproductive axis along with growth and development in seasonally breeding birds.

Disclosures: **E. Alenciks:** None. **K. Frazier:** None. **A. Porter:** None. **G. Fraley:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 613.06/S1

Topic: E.01. Neuroendocrine Processes

Title: The neonatal sensorial denervation induced by capsaicin increases the dendritic arborization in the hippocampus of the adult male rat

Authors: C. CORDERO[1], G. HERNANDEZ[1], E. BIVIANO[1], G. FLORES[2], R. REYES[3], U. QUIROZ[1], *C. MORAN[4];
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Abstract: It has been previously shown that sensorial denervation induced by capsaicin (Caps) decreases the total number of sperm, the motility and viability of the rat. This decrease was higher in the right testis. The participation of the neural mechanisms controlling the spermatogenesis is still unknown. There are neural connections between testicles and central nervous system. Some nuclei that have/use this route are the amygdala and hippocampus. The aim of the present study was to analyze the effects of the sensorial denervation induced by capsaicin on the dendritic morphology in the neurons of amygdala (basolateral nucleus) and hippocampus (CA3). Newborn male rats of the CIIZ-V strain were injected with 50 mg/kg Caps dissolved in vehicle: 10 % ethanol, 10 % Tween 80, and 80 % saline solution, or vehicle only (Control group): The animals were sacrificed at 90 days of age. Dendritic morphology and characteristics were measured by using the Golgi-Cox procedure followed by Sholl analysis. The dendritic morphology did not affect the amygdala. Interestingly the dendritic length and order was higher in the right hippocampus in the denervated animals. Our results suggest that the lack of the sensorial innervation in the testicles leads to asymmetrical response in the dendritic morphology. This response is higher in the right hippocampus and may explain the changes observed in the spermatogenesis of left testicle.

Disclosures: C. Cordero: None. **G. Hernandez:** None. **E. Biviano:** None. **G. Flores:** None. **R. Reyes:** None. **U. Quiroz:** None. **C. Moran:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 613.07/S2

Topic: E.01. Neuroendocrine Processes

Support: CAPES-BRAZIL

FAPESP-BRAZIL

Title: Interaction of leptin, nitric oxide and neuropeptide Y to control the female reproductive function: modulation by estrogen and food condition

Authors: *L. OLIVEIRA, C. R. FRANCI;
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Abstract: Leptin action on hypothalamus-pituitary-gonad axis is mediated by nitric oxide (NO) and neuropeptide Y (NPY). NPY action to control food intake may also be mediated by NO. The control of reproductive function and food intake involves medial preoptic area (MPOA) and arcuate nucleus (Arc), in which were identified neurons that co-express NOS (nitric oxide synthase)-leptin and NOS-NPY. Our aim was assess whether leptin action on reproductive function may be controlled by interaction between NPY and NO as well the effect of different metabolic conditions, and of estrogen. **Methods:** Wistar rats were subjected to ovariectomy and stereotaxic implantation of intracerebroventricular (icv) cannula, a week before the experiment. From the fifth day, they were treated with estradiol cypionate (10 µg / rat) or vehicle (vegetable oil, 0.1 ml / rat). One group was kept fasting for 48 hours before the experiment and the other normally fed. On the day of experiment the animals received icv microinjection of L-NAME (500µg/1µl; Sigma) or vehicle, and an hour later received isotonic saline (control) or leptin (3µg/1µl) icv microinjection. After two hours they were perfused to remove the encephalon. MPOA and Arc were microdissected to assess the NPY and FOS expression by immunohistochemistry. **Results**: We found that in fasting state, the number of active NPY neurons (coexpression FOS-NPY) increased in the ARC and the MPOA, being more evident in Arc, mainly in animals treated with estrogen. In the normal feeding occurs a similar response to the fasting, but the effect of blocking of the NO activity seems to be less pronounced. Leptin treatment caused a considerable decrease in that number, especially in animals without estrogen replacement. The same happened in the treatment with L-NAME, but more evident in animals with replacement, even in fasting, when leptin is low, the number of active NPY neurons decreases, indicating the participation of NO neurons in this communication, mostly in the presence of estrogen. In the treatment with L-NAME and leptin, the number of active NPY neurons also decreased mainly in animals treated with estrogen. This suggests that leptin icv could be influencing this activation through other pathways in the presence of estrogen, moreover in treatment with L-NAME, low leptin has not been able to activate a large number of NPY neurons with blockade NO neurons. Therefore, in fasting situation seems to exist a communication line leptin - NO - NPY, in the MPOA and mainly in Arc, regions involved in the control of reproductive function and food intake, especially in estrogen presence.

Disclosures: **L. Oliveira:** None. **C.R. Franci:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 613.08/S3

Topic: E.01. Neuroendocrine Processes

Title: RFRP-3 stimulates the male mouse reproductive axis

Authors: ***C. ANCEL**, J. S. KIM, M. INGLIS, G. M. ANDERSON;
Dept. of Anat., Ctr. For Neuroendocrinology, Dunedin, New Zealand

Abstract: In 2000, gonadotrophin-inhibitory hormone (GnIH) was discovered in birds and shown to inhibit gonadotrophin secretion (Tsutsui et al. 2000). The mammalian ortholog was concurrently discovered in humans and rats and termed RFamide-related peptide-3 (RFRP-3) (Hinuma et al. 2000). Since then, a number of studies have aimed at determining the involvement of RFRP-3 in the regulation of reproduction in various mammalian species, including rats (Johnson et al. 2007, Murakami et al. 2008, Pineda et al. 2010), hamsters (Kriegsfeld et al. 2006, Ancel et al. 2012, Ubuka et al. 2012), sheep (Clarke et al. 2008, Sari et al. 2009, Caraty et al. 2012), and cattle (Kadokawa et al. 2009). This plethora of results has underlined the species- and sex-specific effects of RFRP-3 on the reproductive axis, through the analysis of LH section in most cases. However, a comprehensive investigation of the role of RFRP-3 in the regulation of the mouse gonadotrophic axis remains to be carried out, in part because of the difficulty in taking repeated LH measurements from this species. In this study, we performed an extensive analysis of the effects of RFRP-3 on LH secretion in male C57BL/6 mice. Using a repeated tail tip blood sampling method combined with a highly sensitive ELISA, RFRP-3 dose-dependently stimulated LH secretion in mice when injected centrally (0.5-5 nmol/mouse), but had no effect when administered peripherally (5-50 nmol). In cultured HEK293 cells transfected with the human KISS1R, RFRP-3 showed some affinity to KISS1R and was able to potentiate the effects of kisspeptin, but did not show agonism alone. This potentiating effect may occur through allosteric modulation, although further studies are required. To conclude, our results show that RFRP-3 can stimulate the reproductive axis in male mice, as has been shown in hamsters (Ancel et al. 2012, Ubuka et al. 2012). Thus, the idea that RFRP-3 and kisspeptin exert opposing effects is likely to be overly simplistic.

Disclosures: **C. Ancel:** None. **J.S. Kim:** None. **M. Inglis:** None. **G.M. Anderson:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 613.09/S4

Topic: E.01. Neuroendocrine Processes

Title: Winter is coming: Linking seasonal cues to reproduction in the mouse

Authors: *M. J. BEYMER[1], C. SÁENZ DE MIERA[1], D. HAZZLERIG[2], V. SIMONNEAUX[1]; [1]Inst. des Neurosciences Cellulaires et Intégratives, Univ. of Strasbourg, Strasbourg, France; [2]Dept. of Arctic and Marine Biol., Univ. of Tromsø, Tromsø, Norway

Abstract: The proper timing of reproduction is an essential factor for the continuation of a species. The Arginine-Phenylalanine-amide (RF-amide) family of peptides is a class of hypothalamic neuropeptides that have been implicated in many physiological regulatory processes, including nociception, stress response, energy metabolism, as well as reproduction. Two members of this family, in particular, have been shown to regulate the hypothalamic-pituitary-gonadal (HPG) axis. Kisspeptin, is expressed by neurons in the arcuate (ARC) and medial preoptic (MPN) nuclei. Release of kisspeptin from these neurons can strongly activate the HPG axis. RF-amide related peptides (RFRP-1 and -3), are expressed in neurons located in and around the dorso- and ventro-medial hypothalamic nuclei. RFRP neurons were original discovered in birds as a potent inhibitory factor of the HPG axis; however this role seems to be less the case in mammalian species where the specific actions of RFRP-3 are species-, sex-, and photoperiod-dependent. The central pathways through which seasonal cues are able to regulate reproductive capacity are still mostly unknown; however recent findings suggest that RFRP and kisspeptin may be involved in this process. In order to fully elucidate the photoperiodic pathways involved in the transduction of seasonal cues onto the reproductive axis we are using several strains of mice with different melatonin profiles: C57BL/6J, which are melatonin-deficient, CBA, which are melatonin-proficient, and MSM/Ms, which are also melatonin-proficient. We placed male mice of all genotypes in either short day (LD 8:16) or long day (LD 16:8) conditions to determine the effect of the presence or absence of melatonin on RF-amides. Both CBA and C57 males showed no significant changes in body weight, paired testes weight, or seminal vesicle weight in response to different photoperiodic conditions. Interestingly, in short day adapted CBA males there was a decrease in *Rfrp* expression as compared to long day adapted CBA males, whereas there was no change in *Rfrp* expression in C57 males in response to either photoperiod. This is in concordance to what is found in classical seasonal breeders adapted to short day conditions where there is a reduction in hypothalamic *Rfrp* expression. It is clear from

these findings that the RFRP system in mice is still sensitive to seasonal cues in the form of melatonin secretion. Furthermore, since we do not see a response of the testes in CBA mice due to changing photoperiods, it is tempting to conclude that there is another central factor, a likely candidate being kisspeptin, in non-seasonal breeders blocking the full transduction of seasonal cues onto the HPG axis.

Disclosures: **M.J. Beymer:** None. **C. Sáenz de Miera:** None. **D. Hazzlerig:** None. **V. Simonneaux:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

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Program#/Poster#: 613.10/S5

Topic: E.01. Neuroendocrine Processes

Support: FAPEMIG

FAPESP

CNPq

PRPq-UFMG

Title: KNDy neurons are activated by estradiol during the preovulatory surges of luteinizing hormone and prolactin in female rats

Authors: ***R. E. SZAWKA**[1], R. ARAUJO-LOPES[1], R. G. L. BERNARDES[1], F. L. M. BELLO[1], P. C. HENRIQUES[1], N. S. S. AQUINO[1], C. R. FRANCI[2];
[1]Univ. Federal De Minas Gerais (UFMG), Belo Horizonte, Brazil; [2]Dept. de Fisiologia, Univ. de São Paulo, Ribeirao Preto, Brazil

Abstract: Central kisspeptin is critical for luteinizing hormone (LH) secretion and fertility in mammals. Kisspeptin, neurokinin and dynorphin (KNDy) neurons in the arcuate nucleus of hypothalamus (ARC) are involved with LH and prolactin (PRL) secretion, but their functional roles in the secretion of these hormones remain poorly understood. Here we used dual label immunohistochemistry to investigate the activity of KNDy neurons associated with changes in LH and PRL secretion in male and female rats under different hormonal conditions. Cycling rats were perfused on the days of diestrus (n = 6), morning of proestrus (n = 6), late afternoon of proestrus (n = 5), and estrus (n = 6). The number of kisspeptin-immunoreactive (ir) neurons in

the ARC was lower on proestrus and estrus compared with diestrus ($P < 0.01$). Conversely, the percentage of kisspeptin-ir neurons expressing c-Fos (anti-c-Fos Ab-5, Calbiochem) was 45% higher on the afternoon of proestrus ($P < 0.05$), when the preovulatory surges of LH and PRL occur. These results were further confirmed in an additional analysis using a different c-Fos antibody (anti-c-Fos K-25, Santa Cruz Biotechnology), which showed the same response of increased activity of KNDy neurons on proestrous afternoon ($P < 0.01$). In male rats ($n = 6$-8), the number of kisspeptin-ir neurons in the ARC was lower than in diestrous females and c-Fos expression in KNDy neurons was low and unchanged between morning and afternoon ($P = 0.68$). Ovariectomized (OVX) rats were treated with oil (OVX; $n = 8$ per group), estradiol (OVX+E; $n = 7$ per group) or estradiol and progesterone (OVX+EP; $n = 6$-7) and perfused in the morning or late afternoon. The number of kisspeptin-ir neurons in the ARC was reduced in OVX+E and OVX+EP rats compared with OVX rats at all time points evaluated ($P < 0.05$). On the other hand, associated with the estradiol-induced afternoon surges of LH and PRL, the expression of c-Fos in KNDy neurons was increased by approximately 50% at 12:00 h ($P < 0.01$) and 18:00 h ($P < 0.05$) in OVX+E rats and only at 12 h ($P < 0.01$) in OVX+EP rats. We provide evidence of a dual effect of estradiol on the regulation of KNDy neurons. Estradiol reduces the expression of kisspeptin in the ARC as part of the negative feedback effect on LH secretion. Concurrently, however, estradiol induces an afternoon rise in the activity of the remaining population of KNDy neurons, suggesting an increase of kisspeptin release at specific synapses by the time of the estradiol-induced surges of LH and PRL. Thus, our findings reveal a novel aspect of the estrogen regulation of KNDy neurons, which expands our knowledge of the neural control of gonadotropin secretion and fertility.

Disclosures: **R.E. Szawka:** None. **R. Araujo-Lopes:** None. **R.G.L. Bernardes:** None. **F.L.M. Bello:** None. **P.C. Henriques:** None. **N.S.S. Aquino:** None. **C.R. Franci:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: E.01. Neuroendocrine Processes

Support: CONACYT-128392

CONACYT-153627

Fundación Beltran-Morgado para el Avance y Difusión de la Neurociencia en Veracruz.

Title: Colocalization of substance P receptor and gonadotropin-releasing hormone (GnRH) in hypothalamic mice neurons

Authors: *R. DÍAZ ESCÁRCEGA[1], A. E. SOSA-ESCALANTE[1], M. L. LOPEZ-MERAZ[2], L. BELTRAN-PARRAZAL[2], C. MORGADO-VALLE[2];
[1]Doctorado en Investigaciones Cerebrales, [2]Ctr. de Investigaciones Cerebrales, Univ. Veracruzana, Xalapa, Mexico

Abstract: The participation of substance P (SP) in the modulation of the Hypothalamic-Pituitary-Gonadal (HPG) axis has been already documented. However, is still incompletely understood whether SP modulation occurs at hypothalamic, pituitary and/or gonadal levels. The HPG axis is driven by the pulsatile secretion of gonadotropin-releasing hormone (GnRH). GnRH is synthesized by a diffuse group of hypothalamic neurons (GnRHergic neurons) terminating in the median eminence (ME). Previously, we have shown *in vitro* that SP increases the firing frequency of GnRHergic immortalized hypothalamic neurons. Furthermore, histological studies in the human hypothalamus show the presence of fibers immunoreactiveto SP juxtaposed with cell bodies of GnRHergic neurons. In this study we tested the hypothesis that the SP receptor, i.e., the neurokinin 1 receptor (NK1R)colocalizes with GnRH inhypothalamus neurons. We performed double immunofluorescent staining against NK1R and GnRH in coronal slices of mouse hypothalamus. Our results suggest that thestimulation exerted by SP on GnRHergic neurons is probably mediated by NK2 or NK3 receptors and not through the NK1R.

Disclosures: R. Díaz Escárcega: None. **A.E. Sosa-Escalante:** None. **M.L. Lopez-Meraz:** None. **L. Beltran-Parrazal:** None. **C. Morgado-Valle:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 613.12/S7

Topic: E.01. Neuroendocrine Processes

Support: NIH RO1 HD039916 (RLG)

Title: Neuromedins U and S differentially regulate pulsatile LH and prolactin secretion and are expressed in the supraoptic and paraventricular nuclei in ewes

Authors: *P. GRACHEV, M. VALENT, R. L. GOODMAN;
Dept. of Physiol. and Pharmacol., West Virginia University, Sch. of Med., Morgantown, WV

Abstract: Prolactin (PRL) secretion is elevated annually during long days and is stimulated by estradiol, while pulsatile LH secretion is subject to negative feedback effects of gonadal steroids and photoperiodic suppression. We have recently demonstrated the biphasic effect of central administration of NMU-8, a synthetic peptide the sequence of which resembles the receptor-binding portion of endogenous ovine neuromedins U and S, on LH pulse amplitude in ewes - stimulatory in ovary-intact and inhibitory in ovariectomized sheep. In light of the differential regulation of prolactin and LH, we proposed that NMU-8 would have converse effects on PRL pulse amplitude. To test this hypothesis, we examined the effects of intracerebroventricular administration of NMU-8 on PRL levels in frequently sampled blood from anestrous or ovariectomized ewes. Immunohistochemistry, utilizing a polyclonal antibody raised in rabbit against NMU-8, was performed as a first step in exploring the localization of endogenous ovine neuronal populations expressing neuromedins U and S. Contrary to our hypothesis, NMU-8 failed to affect PRL pulse amplitude in either anestrous or ovariectomized ewes, but did exert significant biphasic influence over PRL pulse frequency: inhibitory in ovary-intact anestrous and stimulatory in ovariectomized ewes. Discrete populations of neuromedin U/S-immunoreactive soma were localized to the supraoptic (including auxiliary supraoptic) and paraventricular nuclei. These are the first data in sheep that detail effects of central neuromedin U/S signaling on pulsatile PRL secretion and the hypothalamic expression of endogenous ovine neuromedins U and/or S.

Disclosures: **P. Grachev:** None. **M. Valent:** None. **R.L. Goodman:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

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Program#/Poster#: 613.13/S8

Topic: E.01. Neuroendocrine Processes

Support: ANR-13-BSU1-001

Title: Comparative study of the RFRP system in male and female Syrian hamster

Authors: *J. B. HENNINGSEN[1], V. SIMONNEAUX[2], J. D. MIKKELSEN[3], V.-J. POIREL[2], F. GAUER[2];
[2]Melatonin and Seasonal Rhythms, [1]Inst. of Cell. and Integrative Neurosci., Strasbourg, France; [3]The Neurosci. Center, Rigshospitalet, Neurobio. Res. Unit, Copenhagen, Denmark

Abstract: Hypothalamic RF-(Arg-Phe) related peptides (RFRP-1 and -3) are considered to play a role in the (seasonal) regulation of reproduction and their expression is strongly down-regulated by the pineal hormone melatonin in short photoperiod. RFRP-3 stimulates reproductive activity in male Syrian hamsters; however the effects of the peptides depend on species and gender. This study aimed at comparing the RFRP system in male and female Syrian hamsters in long and short photoperiod in order to investigate the neuroanatomical basis of these differential effects. Moreover, we evaluated the effects of intracerebroventricular administration of RFRP-3 in female Syrian hamsters. The neuroanatomical distribution of RFRP neurons and fibers, revealed using an antiserum recognizing RFRP-1 and -3, as well as GPR147 mRNA, are similar in male and female Syrian hamsters. RFRP neurons are mainly found in the dorso/ventromedial hypothalamus while RFRP projections and GPR147 mRNA are observed in the preoptic area, anteroventral-periventricular nucleus, suprachiasmatic nucleus, paraventricular nucleus, bed nucleus of stria terminalis, ventromedial hypothalamus, habenular nucleus and the arcuate nucleus. The number of RFRP neurons is higher in females than in males, and in both sexes, the number of RFRP neurons is reduced in short as compared to long photoperiod. GPR147 mRNA levels are higher in females than in males and is down-regulated in short photoperiod, with a stronger decrease in females than in male. Interestingly, the number of RFRP-positive fibers in the anteroventral periventricular nucleus is higher only in females adjusted to short photoperiod. Chronic intracerebroventricular administration of RFRP-3 decreases the gonadal size of sexually active female hamsters, whereas in SP-adapted females, RFRP-3 potently stimulates gonadal size despite photoinhibitory conditions. RFRP and its receptor GPR147 are down-regulated in short photoperiod in both male and female Syrian hamster. Moreover, our results suggest that the RFRP system is particularly important in females with a distinct role in the anteroventral-periventricular nucleus, possibly in the regulation of the pre-ovulatory LH surge via kisspeptin neurons. The effect of RFRP-3 in female Syrian hamsters depends on the reproductive state of the animal and interestingly, RFRP-3 reactivates the reproductive axis in sexual inactive animals despite photoinhibitory conditions.

Disclosures: **J.B. Henningsen:** None. **V. Simonneaux:** None. **J.D. Mikkelsen:** None. **V. Poirel:** None. **F. Gauer:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

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Program#/Poster#: 613.14/S9

Topic: E.01. Neuroendocrine Processes

Support: FSU College of Medicine

Title: A transcriptomic analysis of the estrous cycle in 4 regions of the mouse brain

Authors: *L. M. DICARLO, C. M. VIED, R. S. NOWAKOWSKI;
Biomed. Sci., Florida State Univ. Col. of Med., Tallahassee, FL

Abstract: For many years biomedical research, and in particular neuroscience research, has often focused on male subjects. Female subjects have frequently been excluded due to the perceived complications of the hormonal changes across the estrous cycle and the potential need to include the appropriate control groups. We utilized transcriptomic analysis of the hypothalamus, hippocampus, neocortex, and cerebellum of female C57BL/6J (B6) mice to examine changes in gene expression in the female mouse brain. The changes in gene expression between brain regions (n=12/brain region) and changes in gene expression within each brain region as a result of the estrous cycle (n=3/stage/tissue) were performed using the same animals. Not surprisingly, there are ~10,000 differentially expressed genes (DEGs) between the hypothalamus, hippocampus, neocortex, and cerebellum at a false discovery rate (FDR) less than 0.05. The hippocampus vs. cerebellum (n=10,610) and neocortex vs. cerebellum (n=10,464) comparisons have the most DEGs and the hippocampus vs. neocortex (n=9,166) comparison has the least. In contrast to the ~10,000 DEGs between brain regions, within each brain region there are fewer than 70 stage-specific DEGs (FDR<0.05) as a result of the estrous cycle. The hippocampus has the most DEGs (n=67), followed by the neocortex (n=55), hypothalamus (n=53), and cerebellum (n=20). Genes encoding hormones or hormone precursors that are significant DEGs in only the hypothalamus are potential candidates to be the source of changes in downstream gene expression. Six genes in the brain region-specific comparisons (Oxt, Pomc, Esr1, Ghrh, Hcrt, Trh) and five genes in the stage-specific comparisons (Oxt, Hcrt, Gh, Prl, Pitx2) fulfill these criteria. The interactions of potential candidate genes on downstream processes within the hypothalamus and between the 4 brain regions are part of ongoing analyses. This dataset demonstrates that the differences between brain regions overwhelm changes in gene expression as a result of the estrous cycle. We expect that our results will be a useful guide for researchers in the field of neuroscience in incorporating females in future experiments as well as shedding light on the interactions of hormones and gene expression in different brain regions.

Disclosures: **L.M. Dicarlo:** None. **C.M. Vied:** None. **R.S. Nowakowski:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 613.15/S10

Topic: E.01. Neuroendocrine Processes

Title: Induction of the rat luteinizing hormone (LH) surge activates pubertally born cells whereas blocking cell proliferation during puberty or adulthood blunts the LH surge

Authors: *M. A. MOHR[1], L. L. DONCARLOS[2], C. L. SISK[1];
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Abstract: The female rodent brain goes through extensive remodeling during puberty, adding new neurons, glia, and microglia to the anteroventral periventricular nucleus of the hypothalamus (AVPV). The AVPV regulates the preovulatory surge of gonadotropin hormone releasing hormone (GnRH) and thus the pituitary surge in luteinizing hormone (LH), the primary trigger of ovulation, and a pivotal event in reproduction. We asked whether cells added to the AVPV during puberty are among those cells active during the LH surge, and whether cells added to the AVPV during or after puberty are necessary for generation of an LH surge. Expt 1: Postnatal day (P) 28 female Sprague-Dawley rats received 4 wks of bromodeoxyuridine (BrdU; 4.5 µg/l in artificial cerebrospinal fluid, aCSF; via ICV cannulas & minipumps) to identify newly born cells. On P56, all females were OVX'd and 1w later a surge was induced with sc injections of estradiol benzoate (EB, 40 µg/kg in sesame oil) on 2 consecutive days followed by progesterone (P, 2 mg/kg, sc, in sesame oil) the next day. Age-matched controls received oil injections. All rats were perfused ~6 hrs after P, a time when both Fos expression in the AVPV and LH secretion were expected to be high. Immunofluorescence for both BrdU and Fos was performed and the proportion of BrdU-immunoreactive (-ir) cells that were Fos-ir was assessed in the AVPV. In EB+P treated animals, ~32% of pubertally born cells in the AVPV were active during the LH surge, whereas only ~8% were active in the absence of hormones. Expt 2: Both pubertal (P28) and adult (~P60) female rats were treated for 4 weeks with the cell proliferation inhibitor, cytosine β-d arabinofuranoside (AraC; 33 µg/µl ICV in a solution of BrdU in aCSF, as above). Age-matched controls received ICV vehicle. Rats treated during puberty were OVX'd on P55-56; those treated as adults were OVX'd on P92-93. An LH surge was induced ~1-2 wk after the end of ICV infusions. Blood samples were taken every 0.5-1 hr for 8 hr on the day of the surge, and RIA for LH was performed. A week later, another surge was induced and animals were perfused at the time of the expected surge, as above. AraC treatment decreased the total number of BrdU-ir cells by 40% and 81%, rats treated during puberty or adulthood, respectively. AraC treatment also delayed by ~40 min and blunted the LH surge (37% and 62% reduction in the peak [LH] in rats treated during puberty or adulthood, respectively), without changes in body weight or overall health. Remodeling of the AVPV during puberty followed by ongoing turnover of cells during adulthood thus may support hormone positive feedback and the generation of the LH surge.

Disclosures: **M.A. Mohr:** None. **L.L. DonCarlos:** None. **C.L. Sisk:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

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Program#/Poster#: 613.16/S11

Topic: E.01. Neuroendocrine Processes

Support: NSF grant IOS1121691

NIH grant T32 HD007133

Title: The trithorax group complex counteracts the repressive effect of the polycomb group at puberty by promoting an active chromatin state at key gene promoters

Authors: *C. A. TORO[1], A. LOMNICZI[1], H. WRIGHT[1], A. SHILATIFARD[2], S. R. OJEDA[1]; [1]Div. of Neurosci., Oregon Hlth. & Sci. Univ. (OHSU), Beaverton, OR; [2]Feinberg Sch. of Med., Northwestern Univ., Chicago, IL

Abstract: The initiation of mammalian puberty requires a diurnal increase in pulsatile gonadotropin releasing hormone (GnRH) secretion from the hypothalamus. This change results from coordinated changes in the activity of gene networks that lead to a synchronized loss of transsynaptic inhibition and gain of transsynaptic/glial excitatory inputs to GnRH neurons. A major regulatory event controlling this process appears to be a mechanism of transcriptional repression. The Polycomb group (PcG) of transcriptional silencers acting within the arcuate nucleus (ARC) of the hypothalamus, has been shown to prevent the premature initiation of female puberty by silencing at least one gene (Kiss1) involved in the pubertal control of pulsatile GnRH release. At puberty, key PcG proteins are evicted from the Kiss1 promoter and this eviction is accompanied by increased abundance of histone post-translational modifications (PTMs) either catalyzed by, or associated to, the Trithorax (TrxG) group of transcriptional activators. To determine if the TrxG complex is an epigenetic component of the transcriptional program controlling puberty we performed a series of studies in female rats. Double fluorescent *in situ* hybridization revealed that key components of the TrxG complex, including the COMPASS genes Set1a and Set1b and the COMPASS-like genes Mll1, Mll2, Mll3 and Mll4 are expressed in ARC kisspeptin neurons. Quantitative PCR demonstrated that the expression of Set1a, Mll1 and Mll3, in addition to the gene encoding UTX, increases in the ARC before puberty. UTX demethylates histone 3 trimethylated at lysine 27 (H3K27me3) and partners with Mll3 to activate distal enhancers. Chromatin immunoprecipitation (ChIP) assays showed that the association of both MLL1 (required for the circadian activation of promoters) and Mll3 (that in conjunction with UTX activates distal enhancers) increase at the regulatory regions of the

puberty-activating genes Kiss1 and Tac2 during juvenile development (PND21-28). We further observed that as the association of these TrxG proteins to the Kiss1 and Tac2 promoters increases, there is an increase in the abundance of histone 3 dimethylated at lysine 4 (H3K4me2), a PTM associated with gene activation. The presence of both a PcG and a TrxG system of epigenetic regulation in ARC kisspeptin neurons, and their opposite pattern of association to the Kiss1 and Tac2 regulatory regions during prepubertal development suggests that a switch from epigenetic repression to activation within these neurons underlies the developmental process by which GnRH release increases by late juvenile development to bring about the pubertal process.

Disclosures: C.A. Toro: None. **A. Lomniczi:** None. **H. Wright:** None. **A. Shilatifard:** None. **S.R. Ojeda:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

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Topic: E.01. Neuroendocrine Processes

Support: FAPESP

CNPq

Title: Estradiol is the major ovarian steroid involved in the transcriptional e translational regulation of kisspeptin system in the preoptic area of female rats

Authors: *C. M. LEITE[1], B. KALIL[2], E. T. UCHOA[2,3], J. ANTUNES-RODRIGUES[2], L. L. K. ELIAS[2], J. A. ANSELMO-FRANCI[1];
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Abstract: Kisspeptin neurons in the antero periventricular region of the preoptic area (POA) are known to be are regulated by ovarian steroids and comprise the major stimulatory input to gonadotrophin-releasing hormone (GnRH) neurons. However, how these ovarian steroids could temporally modulate kisspeptin transcription and translation in the POA is not fully elucidated. Thus, the aim of this study was to determine the time course effects of ovarian steroids on kisspeptin mRNA expression and content in the POA of ovariectomized rats throughout the day. Female Wistar rats were ovariectomized and after 4 days they were treated with oil or oestradiol for 3 days. On the next day, rats treated with oil were injected with oil (OVO), oestradiol

(OVOE) or progesterone (OVOP) and rats treated with oestradiol were injected with oil (OVE) or progesterone (OVEP). In OVO, OVOE and OVOP groups, no changes were observed on kisspeptin mRNA expression and content throughout the day. Compared to OVO group, acute estradiol (OVOE group) or progesterone (OVOP group) treatment did not modify kisspeptin mRNA expression in all time studied, but acute treatment with estradiol or progesterone increased kisspeptin content in the POA at 11 h, 13 h and 17 h. Kisspeptin mRNA expression was not modified throughout in OVE animals, while kisspeptin content in this group was enhanced at 13 h and 15 h. Compared to OVO group, there was an increase in kisspeptin mRNA expression from 10 h to 16 h in OVE group, while POA kisspeptin content increased at 13 h and 15 h. Administration of progesterone in estradiol-primed rats (OVEP) resulted in the same pattern of response for POA kisspeptin mRNA expression and content observed for OVE group. In summary, estradiol treatment for 3 days seems to stimulate the kisspeptin transcript and content in the POA, while acute estradiol only increased kisspeptin content in the POA. On the other hand, progesterone enhanced only kisspeptin content in OVO rats, with no effects in estradiol-primed animals. Thus, these data indicate that estradiol is the major ovarian steroid involved in the transcriptional e translational regulation of kisspeptin system in the POA, while progesterone seems to have minor effects in these responses.

Disclosures: **C.M. Leite:** None. **B. Kalil:** None. **E.T. Uchoa:** None. **J. Antunes-Rodrigues:** None. **L.L.K. Elias:** None. **J.A. Anselmo-Franci:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

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Topic: E.01. Neuroendocrine Processes

Support: HD042645

T32 HD007228

Title: Rapid progesterone signaling in adult female kisspeptin neurons *in vitro*

Authors: *M. A. MITTELMAN-SMITH, A. K. SCOTT, P. E. MICEVYCH;
Neurobio., UCLA, Los Angeles, CA

Abstract: We recently reported the use of immortalized mHypoA51 neurons as a model for anterior hypothalamic (AVPV/RP3V) kisspeptin neurons underlying the LH surge, based on

their estradiol induction of classical progesterone receptor (PR) and kisspeptin (Kiss1). Here, we investigate the role of progesterone (P4) signaling in these cells. P4 synthesized in hypothalamic astrocytes (NeuroP) is critical for normal reproductive function. Blocking local steroidogenesis with aminoglutethimide arrests the estrous cycle and abrogates the LH surge. We hypothesize that E2 and neuroP interact in Kiss1 neurons to induce the LH surge. First, we established a co-culture paradigm with mHypoA51 Kiss1 neurons and primary hypothalamic astrocytes (from adult, female mice). In this co-culture system, media is freely shared, allowing interactive signaling between the two cell types. Following a pretreatment with 1 nM E2, which increases Kiss1 expression, neurons plated on mesh inserts were introduced to primary astrocyte cultures with E2 (astrocytes had no E2 pre-exposure) for a total of 2 hours. During this time, Kiss1 was upregulated dramatically in mHypoA51 neurons, above that seen after E2 (only) treatment. We observed similar results when exposing Kiss1 neurons to astrocyte-conditioned media, confirming that this was a one-way interaction. In order to investigate potential mechanisms through which neuroP might act on Kiss1 neurons, we investigated the activity of Src, a non-receptor tyrosine kinase shown to associate with classical PR localized to the membrane. As assayed by immunocytochemistry, 96.5% of these Kiss1 neurons express Src. A 15 minute exposure to P4 induced phosphorylation of both Src and MAPK in E2-primed Kiss1 neurons. These data indicate one or more functional membrane progesterone receptors in these anterior hypothalamic Kiss1 neurons, which is consistent with western blot data that reveal classical PR and membrane progesterone receptors mPRα and mPRβ in mHypoA51 membranes. Furthermore, these and previous results suggest that E2 primes Kiss1 neurons by inducing both Kiss1 and PR, and that local synthesis of P4 following E2-priming additively stimulates Kiss1 neurons to induce the LH surge.

Disclosures: **M.A. Mittelman-Smith:** None. **A.K. Scott:** None. **P.E. Micevych:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

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Title: Estradiol regulation of A-type potassium currents sculpts the membrane potential response to GABA in arcuate KNDy neurons

Authors: *R. A. DEFAZIO[1], M. A. NAVARRO[3], L. S. MILESCU[3], S. M. MOENTER[2]; [1]Mol. and Integrative Physiol., [2]Mol. and Integrative Physiology, Intrnl. Medicine, Obstetrics and Gynecology, Univ. of Michigan, Ann Arbor, MI; [3]Div. of Biol. Sci., Univ. of Missouri, Columbia, MO

Abstract: Gonadotropin-releasing hormone (GnRH) is the final central output regulating fertility; steroid feedback controls GnRH release. Estradiol-sensitive arcuate kisspeptin neurons stimulate GnRH neurons and may play a role in estradiol feedback regulation of these cells, since GnRH neurons lack estradiol receptor alpha. GABA strongly depolarizes the membrane potential of arcuate kisspeptin neurons from ovariectomized mice treated with estradiol (OVX+E) but this response was blunted in cells from OVX mice. Native intracellular Cl- concentration (15 mM, reversal potential -55 mV) and baseline membrane potential (-75 mV) were not different between groups, ruling out estradiol-dependent changes in these properties. We hypothesized voltage-dependent potassium channels blunt the response to GABA in arcuate kisspeptin neurons from OVX mice. Whole-cell current-clamp recordings were made from neurons in brain slices from OVX and OVX+E mice using a 15 mM Cl- pipet solution (cut 9 - 11AM, record 11AM - 3PM). Input resistance was the same (OVX 852 ± 113 MΩ n=5; OVX+E 672 ± 52 MΩ n=6). We used dynamic clamp to simulate a synaptic input using model parameters based on GABA postsynaptic currents: 10 nS conductance, 7 msec decay time constant, and -55 mV reversal potential. From a baseline membrane potential of -75 ± 0.4 mV (-70 to -79 mV), the membrane potential response to the dynamic clamp synaptic conductance was blunted by 20% in arcuate kisspeptin neurons from OVX vs OVX+E mice (response to 10 nS: OVX 13.0 ± 1.0 mV n=7; OVX+E 15.9 ± 0.9 mV n=6; $p<0.05$). We next tested the hypothesis that A-type voltage-gated potassium channels diminish the response to the GABA conductance using 4-aminopyridine (4-AP, an A-type channel antagonist). The response to GABA was increased in arcuate kisspeptin neurons from OVX mice in the presence of 4-AP ($p<0.05$), with no effect in neurons from OVX+E mice (response to 10nS + 4-AP: OVX 15.9 ± 0.6 mV n=9; OVX+E 15.1 ± 0.4 mV n=6). Input resistance was greater, however, in OVX vs OVX+E in 4-AP (OVX 1055 ± 93 MΩ n=9; OVX+E 818 ± 52 MΩ n=6, $p<0.05$). We tested the effect of decreasing input resistance in neurons from OVX mice by introducing a 0.44 nS leak conductance via dynamic clamp. Despite a 35% decrease in input resistance, the membrane potential response was decreased by only 6% (n=3), suggesting that input resistance alone is insufficient to explain the effect of 4-AP. Our data support the hypothesis that a strong A-type potassium current in arcuate kisspeptin neurons from OVX mice blunts the depolarizing membrane potential response to GABA. Estradiol suppression of this A-type current may play a role in regulating the output of arcuate kisspeptin neurons.

Disclosures: R.A. DeFazio: None. **M.A. Navarro:** None. **L.S. Milescu:** None. **S.M. Moenter:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 613.20/S15

Topic: E.01. Neuroendocrine Processes

Support: NIH Grant HD41469

Title: Bursts-generation mechanisms of AVPV kisspeptin neurons are regulated by the estrous cycle with multiple currents involved

Authors: *L. WANG[1], S. M. MOENTER[1,2,3];
[1]Mol. and Integrative Physiol., [2]Intrnl. Med., [3]Obstetrics & Gynecology, Univ. of Michigan, Ann Arbor, MI

Abstract: Gonadotropin-releasing hormone (GnRH) neurons form the final common pathway for central control of fertility, but lack estrogen receptor alpha (ERα) needed for negative and positive feedback regulation. The anteroventral periventricular area (AVPV) is a likely site of estradiol positive feedback induction of the proestrus GnRH surge. Release of neuropeptides such as kisspeptin is linked with action potential bursts. We tested the hypothesis that burst generation in AVPV kisspeptin neurons differs with estrous cycle stage. AVPV kisspeptin neurons exhibit increased burst firing on the afternoon of proestrus (P, positive feedback) vs diestrus (D, negative feedback). This difference was maintained after blocking fast synaptic transmission, indicating intrinsic mechanisms (bursts/5min, n≥11cells, control, D 17.4±7.4, P 56.4±14.4; blockers, D 0.7±0.3, P 24.8±8.1, $p<0.05$). To study burst-generation mechanisms, depolarizing and hyperpolarizing current injections were done in current-clamp mode. During depolarization, cells fired tonically (instantaneous frequency, IF, 21.4 ± 5.1 Hz, n=25), or fired an initial 3-4 spike depolarization-induced burst (DIB) with a higher IF than tonic cells (113.6 ± 1.0 Hz, n=16, $p<0.001$). Cycle stage did not affect tonic vs DIB firing patterns (tonic vs DIB, D, 69% vs. 31%, n=19; P, 54% vs. 46%, n=22). After hyperpolarizing current injection, most tonic cells (D 62%, n=13; P 75%, n=12) generated rebound bursts (≥2 spikes), but DIB cells only had rebound bursts on proestrus. Ni2+ (100μM), a T-type current (IT) blocker, decreased initial DIB IF (control 106.4±2.8Hz; Ni 46.0±2.4Hz, n=8, $p=0.0008$), and eliminated rebound spikes in most cells (D 7 of 8; P 6 of 7). We used voltage-clamp to study IT. Current density was greater ($p<0.01$) on P vs D from -50 to -30mV with no difference in voltage-dependence between cycle stages, perhaps indicating increased channels in the membrane. This suggests IT may underlie increases in both rebound and depolarization-induced bursts in these cells during positive feedback. All diestrous cells showed IT but only half had rebound bursts, suggesting another channel under cycle regulation plays a facilitatory role to trigger rebound spikes. Voltage ramps

(10mV/s from -80mV) ±TTX (1μM) were used to isolate persistent sodium current (INaP). INaP current density was greater from -52.5 to -42.5 mV ($p<0.01$) on diestrus in cells exhibiting rebound bursts than those without rebound. These observations suggest mechanisms for increased intrinsic bursts in AVPV kisspeptin neurons on proestrus during estradiol positive feedback, and indicate that burst generation is complex, with multiple currents involved.

Disclosures: L. Wang: None. **S.M. Moenter:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: E.01. Neuroendocrine Processes

Support: HD34860

Title: Arcuate kisspeptin-expressing neurons exhibit steroid-sensitive long-term patterns of episodic firing activity in male mice

Authors: *M. RICU[1], S. M. MOENTER[2];
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Abstract: Gonadotropin-releasing hormone (GnRH) neurons form the final common pathway for central regulation of fertility via the episodic release of GnRH, which is modulated by gonadal steroid feedback. The episodic nature of GnRH release suggests synchrony among the GnRH neuronal population but where this rhythm arises is unknown. Further, as GnRH neurons do not express the steroid receptors needed for feedback regulation of GnRH release frequency, where steroid feedback acts centrally to regulate this frequency is also unknown. Kisspeptin neurons of the arcuate nucleus are a potential site for both rhythm generation and steroid feedback integration. Kisspeptin neurons are steroid-sensitive and synapse on GnRH neurons. The kisspeptin-expressing neurons of the arcuate nucleus of the hypothalamus are called KNDy neurons because they coexpress neurokinin B and dynorphin, both of which may also affect GnRH release pattern. KNDy neurons have been postulated to be extrinsic drivers of pulsatile GnRH secretion via release of kisspeptin, which increases GnRH neuron activity and release. The objective of this work was to determine the long-term firing pattern of KNDy neurons and test if this pattern is steroid sensitive in male mice. KNDy neurons were identified by expression of green fluorescent protein driven by the Tac2/NKB promoter. Coronal brain slices (400μm)

were made from adult gonad-intact and castrate (5-10 d before slice preparation) male mice. Spontaneous action potential firing activity of single KNDy neurons was monitored for 1-7h with targeted extracellular recordings. Peaks and nadirs in firing rate were analyzed with the Cluster8 algorithm. KNDy neurons showed repeated episodic peaks in firing activity in both intact and castrated mice. Firing rate of KNDy neurons from intact males was episodic with 0.8±0.1 peaks/h (n=12). This frequency was markedly increased ($p<0.004$) in KNDy neurons from castrate males (1.7±0.3 peaks/h, n=6). A corresponding decrease ($p<0.008$) in interpeak interval from 50.7±4.8 min in intact (n=7) to 30.0±4.1 min in castrate mice (n=6) was observed. Peak firing rate was not different between KNDy neurons from intact (5.6±1.3 Hz) and castrate (4.5±1.7 Hz) mice. Of interest, firing peak intervals in KNDy neurons are strikingly similar to those observed in GnRH neurons (Biol Repro 74:931). Together these observations are consistent with the hypothesis that changes in KNDy activity drive changes in GnRH activity and that steroid sensitivity of this episodic pattern may arise in KNDy neurons. Our next steps are to examine if firing activity is coordinated among KNDy neurons and if KNDy neuron activity is coordinated with GnRH release.

Disclosures: **M. Ricu:** None. **S.M. Moenter:** None.

Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 613.22/S17

Topic: E.01. Neuroendocrine Processes

Title: Morphometric and myelination changes in ARC kisspeptin neurons underlie activation of HPG-axis during breeding season in the adult male rhesus monkey

Authors: H. ZUBAIR[1], S. SHAMAS[1], H. ULLAH[1], T. HUMA[2], S. KIRAN[1], *R. HUSSAIN[1], M. SHAHAB[1];
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Abstract: Recently, kisspetin has been observed to enhance the gonadotropin secretion in rodent and primate species by various expression and functional studies. Kisspeptin has also been shown to play a role in seasonal regulation of the HPG-axis in rodents and sheep. Present study was designed to assess the involvement of kisspeptin signaling in regulating the transition between breeding and nonbreeding seasons by comparing the semi-quantitative expression of the kisspeptin like-immunoreactivity, measurement of the kisspeptin cell body size, myelination

status of the kisspeptin axons and number of close contacts between kisspeptin fibers and GnRH cell bodies in the hypothalamus of the adult male rhesus monkey. Hypothalamic tissues were collected from three free ranging breeding season (September) and two nonbreeding season (June) monkeys and fixed, and stored in 30% sucrose solution. Testicular dimensions were noted and a blood sample was obtained for determination of testosterone levels before euthanization from all animals. This study was approved by the Research Ethics Committee of the Quaid-i-Azam University. Twenty µm thick hypothalamic sections were processed for standard immunocytochemistry procedure using sheep anti human kisspeptin, mouse anti human myelin basic protein (MBP) and rabbit anti GnRH as primary antibodies against kisspeptin, MBP and GnRH, respectively. The immunoreactivities were identified by using Alexa Flour 488 (kisspeptin), Cy3 (MBP) and Texas red (GnRH) labeled specific secondary antibodies. Three consecutive sections (mediobasal hypothalamus) were stained from each animal. Primary antibody omitted control sections were used to check the nonspecific binding of the antibodies. Plasma testosterone levels and testicular volumes were found to be significantly higher in breeding season monkeys as compared to that in non-breeding season monkeys. Increased expression of kisspeptin like-immunoreactive cell bodies and higher number of synaptic contacts between kisspetin fibers and GnRH cell bodies was observed in the arcuate nucleus of the breeding season monkeys while increased kisspeptin cell body diameter and increased thickness of myelin sheath around the axons was quantified in nonbreeding season monkeys. In summary, our results indicate enhanced kisspeptin signaling in the hypothalamus of the breeding season monkeys as compared to the non-breeding season monkeys. Further, degree of myelination and diameter of kisspeptin-ir cell bodies is increased during the non-breeding season. Present results suggest that kisspeptin acts as an arbitrator of the seasonal regulation of the reproductive axis in higher primates.

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Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

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Topic: E.01. Neuroendocrine Processes

Title: Kisspeptin does not affect excitatory postsynaptic currents in supraoptic nucleus neurons from virgin or pregnant rats

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Dept. of Physiol., Univ. of Otago, Dunedin, New Zealand

Abstract: Supraoptic nucleus magnocellular neurosecretory cells (MNCs) project to the posterior pituitary gland where they secrete oxytocin or vasopressin into the circulation in response to action potential firing. During parturition and lactation, oxytocin is released in pulses to stimulate uterine contraction (in parturition) and mammary gland duct contraction to eject milk (in lactation). Despite the importance of these physiological processes, relatively little is known about what initiates and maintains action potential firing in oxytocin MNCs at these times. Previous *in vivo* electrophysiology experiments in our lab have shown that kisspeptin causes a transient excitation of oxytocin neurons in late pregnant rats but not in virgin or early pregnant rats. This suggests that oxytocin neurons become sensitive to kisspeptin during pregnancy, and hence that this might be involved in preparation for parturition. Here, we have recorded from MNCs in rat hypothalamus coronal slices from virgin and late-pregnant rats to determine the mechanisms of excitation of oxytocin neurons in late-pregnant rats. Using whole-cell voltage clamp recording with a holding potential of -60 mV and constant perfusion of 100 μM picrotoxin to block GABA-mediated events and 0.5 μM tetrodotoxin to block action potential-mediated events, we measured miniature excitatory post-synaptic current (mEPSC) frequency and amplitude in response to kisspeptin. We found that mEPSC frequency was lower in late pregnant rats compared to virgin rats (t-test $P = 0.02$). However, kisspeptin did not change mEPSC frequency ($P = 0.70$, two way repeated measures ANOVA) or amplitude ($P = 0.77$) in MNCs from virgin or late-pregnant rats. Furthermore, kisspeptin did not change the mean baseline current ($P = 0.82$) in virgin or late-pregnant rats suggesting that there was no direct effect of kisspeptin on MNCs. These results suggest that the emergence of oxytocin MNC excitation by kisspeptin in pregnancy probably does not occur locally within the brain slice and is likely mediated upstream. However, it is also possible that kisspeptin causes excitation of oxytocin MNCs by altering GABAergic synaptic transmission. Therefore, we are currently investigating whether changes in inhibitory post-synaptic currents occur during kisspeptin administration to MNCs from virgin and late-pregnant rats.

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Poster

613. Hypothalamic?Pituitary?Gonadal Axis: Neural Control

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Topic: E.01. Neuroendocrine Processes

Support: R01-NS38809

R01-NS43330

R01-DK68098

Title: High frequency - induced peptide release governs the synchronization of the arcuate kisspeptin neurons

Authors: ***J. QIU**[1], C. C. NESTOR[1], S. L. PADILLA[2], R. D. PALMITER[2], O. K. RØNNEKLEIV[1,3], M. J. KELLY[1,3];
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Abstract: The pulsatile release of gonadotropin-releasing hormone (GnRH) neurons is necessary for reproductive success. Kiss1 neurons provide critical synaptic input to GnRH neurons; however it has yet to be determined whether Kiss1 afferents generate a synchronous patterned input that facilitates GnRH pulsatility. One population of Kiss1 neurons in the hypothalamic arcuate nucleus (ARC) that co-express neurokinin B (NKB), dynorphin (Dyn) and glutamate, may provide synchronized excitatory drive to GnRH neurons. To explore the possibility of synchronization among Kiss1 neurons, we injected an adeno-associated virus (AAV) that allows Cre-dependent expression of channelrhodopsin 2 (ChR2:YFP) in the ARC of *Kiss1*$^{Cre:GFP}$ mice. A short train of blue light (470 nm) stimuli delivered at a frequencies of ≥10 Hz evoked a slow excitatory postsynaptic potential (slow EPSP) in ARC Kiss1 neurons in hypothalamic slices. The slow EPSP was frequency and duration dependent, and was abolished by perfusing low Ca^{2+}/high Mg^{2+} or TTX. The TTX blockade was rescued by the addition of non-selective K^+ channel blockers 4-AP and TEA, suggesting the slow EPSP was dependent on direct synaptic input from neighboring Kiss1 neurons. Furthermore, the slow EPSP was unaffected by the ionotropic glutamate receptor antagonists CNQX and AP5, but was abrogated by an NKB receptor (NK3R) antagonist and occluded by NKB pretreatment, demonstrating that the slow EPSP was mediated by the Gq-coupled NK3R. Taken together, these findings suggest that NKB-mediated slow EPSPs may play a pivotal role in the prolonged excitation and synchronization of ARC Kiss1 neurons which could potentially drive GnRH pulsatile release.

Disclosures: J. Qiu: None. **C.C. Nestor:** None. **S.L. Padilla:** None. **R.D. Palmiter:** None. **O.K. Rønnekleiv:** None. **M.J. Kelly:** None.

Poster

614. Estrogen Signaling and Cognition

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 614.01/S20

Topic: E.03. Behavioral Neuroendocrinology

Support: NSERC Grant 400212

Title: The rapid effects of estrogens in the medial amydgala on social recognition in female mice

Authors: *P. A. SHEPPARD, J. LYMER, T. KUUN, P. PALETTA, E. CHOLERIS; Psychology, Univ. of Guelph, Guelph, ON, Canada

Abstract: It is becoming well established that estrogens affect different types of learning and memory on a rapid time scale. Specifically, estrogens can affect social recognition in female mice within 40 minutes of drug administration. Improvements in social recognition have been shown with the systemic administration of 17β-estradiol, the estrogen receptor (ER) α agonist, PPT, and the G-protein coupled estrogen receptor 1 (GPER) agonist, G-1, while impairments in social recognition have been shown with the ER β agonist, DPN (Phan et al., 2011; 2012). Although the hippocampus has been shown to mediate these effects, other brain regions are likely involved in the estrogenic facilitation of social recognition. One possible candidate is the medial amygdala, as it has been shown to be necessary for social recognition (Wang et al., 2014), and ER α in the medial amygdala is involved in the estrogenic facilitation of social recognition on a long-term time scale (Spiteri et al., 2010). Thus, we investigated the role of 17β-estradiol, G-1, PPT, and DPN in the medial amygdala in social recognition in ovariectomized female mice. Mice received an infusion (0.5μL/side, rate of 0.2μL/min) of 17β-estradiol (10, 25, 50, 100nM), G-1 (25, 50, 200, 400nM), PPT (25, 50, 100, 150nM), or DPN (25, 50, 100, 150nM) directly into the medial amygdala. Mice were then tested on the social recognition paradigm, consisting of two 5min habituations where two female conspecifics are presented, and one 5min test phase where one of the stimulus mice presented is novel and the other is familiar. The paradigm is completed within 40min of drug administration to investigate the rapid effects of estrogens. Medial amygdala infusions of 50nM G-1 improved social recognition. The experiments with 17β-estradiol, PPT, and DPN are currently underway. Therefore, estrogens, at least via the GPER, in the medial amygdala are involved in the rapid estrogenic facilitation of social recognition in female mice. Supported by NSERC.

Disclosures: P.A. Sheppard: None. **J. Lymer:** None. **T. Kuun:** None. **P. Paletta:** None. **E. Choleris:** None.

Poster

614. Estrogen Signaling and Cognition

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 614.02/T1

Topic: E.03. Behavioral Neuroendocrinology

Support: R01AG0411374

Title: Evidence of ligand-independent activation of estrogen receptor alpha in rat hippocampus

Authors: E. M. GRISSOM, *J. M. DANIEL;
Tulane Univ., New Orleans, LA

Abstract: Previous work by us and others indicates that increased levels of hippocampal estrogen receptor alpha (ERα) are associated with enhanced cognition even in the absence of ovarian or exogenously administered estrogens. *In vitro* evidence indicates that under conditions of low levels of estrogens, growth factors, including insulin-like growth factor-1 (IGF-1) can activate ER and regulate ER-mediated transcription through mechanisms that likely involve modification of phosphorylation sites on ER by cellular kinases. The goal of the current work was to investigate a role for IGF-1 in ligand-independent activation of ERα by IGF-1 in rat hippocampus. Ovariectomized rats received a single icv infusion of IGF-1 and hippocampi were collected 1 h later. IGF-1 increased phosphorylation of ERα at serine 118 (S118), but not at S167, as revealed by Western blotting. Activated ERα bound to estrogen response elements (EREs) recruits coactivators, including steroid receptor coactivator (SRC)-1, that stimulates gene transcription. Therefore, we next measured the impact of IGF-1 on the association of ERα and SRC-1 via co-immunoprecipitation. Rats that received IGF-1 infusions had significantly enhanced ERα -SRC-1 interactions in the hippocampus than those that received control infusions. Collectively results indicate that IGF-1 ligand-independently activates ERα in the hippocampus via phosphorylation at S118 resulting in increased association of ERα with SRC-1. To our knowledge, these data are the first *in vivo* evidence of ligand-independent actions of ER and provide a mechanism by which ERα can impact memory in the absence of ovarian estrogens.

Disclosures: E.M. Grissom: None. **J.M. Daniel:** None.

Poster

614. Estrogen Signaling and Cognition

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Topic: E.03. Behavioral Neuroendocrinology

Support: NSF IOS 13-18490

NIH P30 AG034464, Center on Aging and Policy Studies, Syracuse University

NIH P50AT006268 from NCCAM, ODS, and NCI

Title: Estradiol increases extracellular glucose concentration in the hippocampus of young adult female rats

Authors: *W. WANG, P. E. GOLD, D. L. KOROL;
Dept. of Biol., Syracuse Univ., Syracuse, NY

Abstract: Estrogens promote hippocampus-based learning and facilitate glucose uptake into the brains of ovariectomized rodents. Thus, we hypothesized that estradiol treatments would increase extracellular glucose concentrations in the hippocampus in awake behaving rats. To test this, we used microdialysis to measure extracellular glucose in the hippocampus of three-month-old ovariectomized Sprague-Dawley rats that received either estradiol (4.5 μg/kg) or oil vehicle (s.c.) 24 and 48 hours prior to microdialysis. Microdialysis probes, previously implanted unilaterally in the ventral hippocampus, were used to collect dialysate samples (20 min each) while rats were in a holding container that allowed free movement. Artificial cerebrospinal fluid prepared with six different concentrations of glucose (0.5 mM-3 mM) was infused through the probes while dialysates were collected for off-line assay of glucose concentration. Separate groups of rats were tested for each glucose concentration. The dialysates were later measured for glucose content with an enzymatic assay. Comparisons of [glucose]out vs. [glucose]in for different glucose concentrations in the perfusate generated a Zero-Net-Flux regression line. The concentration where [glucose]in = [glucose]out reflected the extracellular concentration. Rats with estradiol treatment had hippocampal extracellular glucose concentrations of 2.44 ± 0.1 mM whereas extracellular concentrations in oil-treated rats were nearly 25% lower at 1.86 ± 0.16 mM. The higher glucose concentrations associated with estrogens may protect the female hippocampus against glucose depletion during cognitive activity and, by extension, also protect energy availability needed to support cognitive functions during aging. Currently, we are examining whether estrogen treatment to ovariectomized rats protects against experimentally-induced local glucose deprivation in the hippocampus by rapidly providing metabolic substrates such as glucose or lactate to accommodate the depletion. This result would indicate that estrogens create a dynamic energetic state in hippocampus that could protect against metabolic insult. Our findings support a growing literature suggesting that estrogens may benefit hippocampal functioning through modulation of bioenergetics.

Disclosures: W. Wang: None. **P.E. Gold:** None. **D.L. Korol:** None.

Poster

614. Estrogen Signaling and Cognition

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Program#/Poster#: 614.04/T3

Topic: E.03. Behavioral Neuroendocrinology

Support: NIH Grant AG028084

State of Arizona

ADHS and the Arizona Alzheimer's Disease Core

Title: Adding reference memory to a working memory maze task alters the pattern of age-related impairment in rats: Associations with choline acetyltransferase activity in discrete brain regions

Authors: *A. V. PRAKAPENKA[1,3,4], R. HIROI[2,3], M. POISSON[2,3], Z. KIRSHNER[5], A. J. CASTANEDA[2], R. B. GIBBS[5], H. A. BIMONTE-NELSON[2];
[2]Dept. of Psychology, [1]Arizona State Univ., Tempe, AZ; [3]Arizona Alzheimer's Consortium, Phoenix, AZ; [4]Barrow Neurolog. Inst., Barrow Brain Tumor Res. Ctr., Phoenix, AZ; [5]Dept. of Pharmaceut. Sci., Univ. of Pittsburgh Sch. of Pharm., Pittsburgh, PA

Abstract: Rodent studies demonstrate that age-related detriments are particularly pronounced for the ability to handle an increasing working memory load in spatial tasks such as the water radial-arm maze (WRAM). However, the extent of age-related cognitive changes may be impacted by the memory domains required to solve the task. Using the WRAM, in young, middle-aged, and aged rats, our laboratory has noted that as working memory load increases, not only do errors in working memory arms increase, but errors into reference memory arms increase as well. This suggests that working and reference memory are linked and that demanding use of both memory types simultaneously can impact performance outcomes. Here, we tested whether the addition of a reference memory component impacted working memory performance in young (6 mos) vs aged (21 mos) female rats. Four groups were tested. One young and one aged group were tested on an 8-arm WRAM task requiring working memory only, with 7/8 arms containing platform escape. Another young and another aged group were tested on a 12-arm WRAM task that also had 7/12 arms containing platform escape, plus 5 reference memory arms with no platform. Performance comparison of the mazes enables evaluation of age-related changes in the ability to handle a working memory load with or without distinct reference memory requirements. Because there are critical links between the cholinergic system, aging, and performance, choline acetyltransferase (ChAT) activity was assayed in several brain regions after testing. Results showed all rats performed worse in the 12-arm vs the 8-arm maze, and there was a larger age effect in the 8-arm, working memory only, version. Trajectories of learning to handle a working memory load differed by age, and this was impacted by whether the distinct reference memory component was present. Moreover, there was an age-related increase in ventral hippocampus and

frontal cortex ChAT activity. Analyses to parse out relations between the cholinergic system and memory-specific abilities in young versus aged animals are currently being pursued. Understanding region-specific relationships between the cholinergic system and prowess for different memory types may unveil distinct neurocircuitries underlying age-related changes in memory.

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Poster

614. Estrogen Signaling and Cognition

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 614.05/T4

Topic: E.03. Behavioral Neuroendocrinology

Support: NIH 5P50AT006268-05

Title: The effects of the botanical estrogen isoliquiritigenin on cognition in young adult female rats

Authors: ***P. KUNDU**[1], T. TUNUR[2], D. KOROL[2], S. BANDARA[1], S. MONAIKUL[1], W. G. HELFERICH[1], S. SCHANTZ[1];
[1]Univ. of Illinois Urbana-Champaign, Urbana, IL; [2]Syracuse Univ., Syracuse, NY

Abstract: It is well established that estrogens modulate cognition in a task-dependent manner. Estrogen replacement generally improves hippocampus-sensitive learning although this effect can vary with age, stress status, and hormone regimen. Many dietary supplements contain estrogenic compounds, the efficacy and safety of which are poorly understood. This study investigated the efficacy of the commercially available botanical estrogenic compound isoliquiritigenin (ISL) to alter performance on a hippocampus-sensitive metric change in object location (MCOL) task. ISL is a compound found in licorice root that is currently used in over-the-counter dietary supplements. Because the Western diet is high in saturated fat, and high fat diets (HFD) have been shown to negatively impact cognition in rodent models, we also explored whether a HFD would impair performance on this hippocampus-sensitive task and whether ISL could mitigate the negative effects of the HFD. Thus, we included HFD as well as low fat (LFD) groups. Young adult (3-month old) Long-Evans female rats were ovariectomized and exposed to either a HFD (44.8% kcal from fat) or a LFD (17.2% kcal from fat) for five weeks prior to testing. A subset of rats on each diet was exposed to ISL at a concentration of 0.05% of the diet

for three weeks prior to testing. Since estradiol improves performance on the MCOL task, we used an estradiol group as a positive control. Rats in the estradiol group were injected subcutaneously 48 and 24 hours prior to testing with 45 µg/kg of estradiol. In the MCOL task, rats were allowed to explore two objects in a black Plexiglas® chamber measuring 28x28x21 inches. Exploration time was recorded for three 5-min trials with a 3-min inter-trial interval in the rat's home cage. For the fourth 5-min trial, the objects were moved closer together and exploration time was again recorded. An increase in object exploration time in the final trial suggests that the rat detected the change in object locations. ISL led to a significant increase in exploration time in the final trial relative to the third trial. To a lesser degree, estradiol also increased object exploration time on the final trial. Diet had no effect on its own and did not interact with ISL exposure. In this study we showed that ISL improved performance on a hippocampus-sensitive task that depends on the natural tendency to explore novel objects but avoids food restriction or aversive stimuli. We are currently using Western blot analysis to assess the levels of estrogen-sensitive synaptic proteins in the hippocampus, which could provide clues as to the mechanism of action for the improved performance in ISL exposed animals. Supported by NIH 5P50AT006268-05.

Disclosures: P. Kundu: None. **T. Tunur:** None. **D. Korol:** None. **S. Bandara:** None. **S. Monaikul:** None. **W.G. Helferich:** None. **S. Schantz:** None.

Poster

614. Estrogen Signaling and Cognition

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Topic: E.03. Behavioral Neuroendocrinology

Support: NIH Grant AG028084

State of Arizona

ADHS and the Arizona Alzheimer's Disease Core

Title: Excreted but not forgotten: Estriol effects on spatial working and reference memory task performance in middle-aged ovariectomized rats

Authors: *G. A. STONEBARGER[1,2], S. V. KOEBELE[1,2], H. A. BIMONTE-NELSON[1,2]; [1]Psychology, Arizona State Univ., Tempe, AZ; [2]Arizona Alzheimer's Consortium, Phoenix, AZ

Abstract: Many common forms of hormone therapy (HT) for menopausal and post-menopausal women contain estrogens that are not native to women. Recently, there has been a focus on HT options during menopause that contain bioidentical (naturally and endogenously circulating) hormones. The three primary bioidentical, endogenously circulating estrogens in women and rats are 17β-estradiol, estrone, and estriol. Of these, estriol is the only estrogen that is not currently used as a primary estrogenic component in commonly prescribed hormone therapy treatments in the United States. Presumably due to its status as a "weak estrogen," meaning that it has a low estrogen receptor binding affinity compared to 17β-estradiol, it has not been cognitively characterized. Due to estriol's previously observed neuroprotective effects on the hippocampus *in vitro*, we propose estriol as a promising candidate for HT that may exhibit a positive cognitive profile. In order to begin to characterize estriol's cognitive effects, female middle-aged Fischer-344 rats were given a tonic low- or high- dose of estriol or a vehicle, then tested on a 15 day water radial-arm maze and 5 day Morris water maze. Water radial-arm maze results indicate that both the low- and high- dose estriol groups were impaired on working memory performance compared to vehicle animals, but there were no differences among groups on the Morris water maze. However, uterine weight - an indicator of estrogenic stimulation - and body weight analyses indicated that both doses were likely high enough to induce supraphysiological estriol levels. Cognitive performance and health data will be presented and discussed in the context of additional findings testing other bioidentical estrogens, along with contemplations of evaluating lower doses, varied routes of administration, and behavior testing parameters.

Disclosures: G.A. Stonebarger: None. **S.V. Koebele:** None. **H.A. Bimonte-Nelson:** None.

Poster

614. Estrogen Signaling and Cognition

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Topic: E.03. Behavioral Neuroendocrinology

Support: NIH Grant RO1AG041374

Louisiana Board of Reagents Fellowship LEQSF (2012-17)-GF-15

Title: Examination of mechanisms through which estrogen receptor-dependent transcription persists in brains of female ERE-Luc mice lacking ovarian estrogens

Authors: *K. J. POLLARD[1], E. GRISSOM[2], J. DANIEL[2];
[1]Neurosci., [2]Psychology and Neurosci., Tulane Univ., New Orleans, LA

Abstract: We examined the role of ovarian estrogens, neuroestrogens, the extracellular signaling related kinase (ERK) cascade, and the phosphoinositide-3-kinase (PI3K) cascade in the maintenance of estrogen response element (ERE)-dependent transcription across several brain regions using female estrogen receptor (ER) reporter mice, ERE-Luc, which express the luciferase reporter gene under the transcriptional control of the ERE DNA sequence. In an initial experiment, we compared the effect of ovariectomy (OVX) on ERE-dependent transcriptional activity in the uterus to tissue taken from cerebral cortex, hippocampus, and hypothalamus. Levels of ERE-dependent transcription were reduced to negligible levels in uteri of OVX mice as compared to gonadally intact females. Interestingly, levels of luciferase activity across brain regions were not reduced in OVX mice when compared to intact mice, regardless of estrous cycle stage. To investigate mechanisms by which ER-dependent transcription persists in the brain following OVX, a second experiment was conducted. For three days, the ER antagonist ICI (182.780), the aromatase inhibitor letrozole, or vehicle solution was delivered continuously ICV via cannulae connected to osmotic minipumps. ICI significantly reduced ERE activity in all brain regions examined, confirming that transcription was ER-dependent. The extent of attenuation of ERE activity observed after letrozole treatment varied by brain region, suggesting that neuroestrogens differentially contribute to ER-dependent transcription in each of these brain regions. Collectively these data show that (1) ERE-dependent transcriptional activity in the brain is not reduced following removal of ovarian estrogens and (2) the influence of brain-derived estrogens varies across brain regions. In the final experiment experiment, mice were given ICV infusions of ERK or PI3K inhibitors to determine the contribution of these kinase cascades to ERE-dependent transcriptional activity across brain regions. Results of this experiment are pending.

Disclosures: **K.J. Pollard:** None. **E. Grissom:** None. **J. Daniel:** None.

Poster

614. Estrogen Signaling and Cognition

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Topic: E.03. Behavioral Neuroendocrinology

Support: NIH Grant AG028084

State of Arizona

ADHS and the Arizona Alzheimer's Disease Core

Title: An orderly interaction? Maze order impacts the outcome of estrogen effects on memory

Authors: *S. V. KOEBELE[1,2], A. M. QUIHUIS[1,2], C. N. LAVERY[1,2], Z. M. T. PLUMLEY[1,2], H. A. BIMONTE-NELSON[1,2];
[1]Psychology, Arizona State Univ., Tempe, AZ; [2]Arizona Alzheimer's Consortium, Phoenix, AZ

Abstract: Aging and the loss of ovarian hormones are each associated with memory decline for spatial navigation. In females, there is evidence that estrogen administration during a critical window of opportunity during middle-age may attenuate age-related memory decline. This beneficial effect of estrogens is thought to be dependent upon a variety of factors, including dose, timing, and route of administration. Additionally, the order in which animals experience a battery of maze tasks may impact performance and flexibility to shift from one task to another. Indeed, our laboratory has shown that female rats with prior maze experience transfer the benefits of practice to a novel spatial memory task. Here, we evaluated the effect of 17β-estradiol treatment and maze task learning order on spatial memory performance during middle-age. Eleven-month-old Fischer-344-CDF female rats were ovariectomized and received a tonic dose of Vehicle, low 17β-estradiol, or high 17β-estradiol via a subcutaneous mini-osmotic Alzet pump. Animals were trained on the delayed-matching-to-sample water maze (DMS), a low-cognitive demand spatial working and recent memory task, and the water radial-arm maze, a spatial working and reference memory task that involves increasing working memory load capacity as trials progress and is considered to be a more taxing memory task (i.e. high-cognitive demand). Half of the animals were trained on DMS first, and the other half was trained on WRAM first, before each group learned the second task. Results indicate that 17β-estradiol-treated animals that experienced WRAM first learned DMS better than animals without prior maze experience, such that animals with prior maze experience treated with tonic 17β-estradiol made fewer errors on DMS compared to 17β-estradiol-treated animals without prior experience. Divergent memory effects were revealed with respect to WRAM performance. Previous maze experience on DMS did not impart the same beneficial effects of enhanced performance on WRAM compared to animals that had no prior maze experience. Overall, these data indicate that the order in which maze batteries are administered matters, and that 17β-estradiol treatment while learning a complex cognitive task confers an enhanced capacity for learning a novel spatial memory task; however, previous experience on a less cognitively demanding memory task does not enhance learning and memory performance on a novel task to the same extent. Results suggest that 17β-estradiol exposure and high-memory demand performance are important factors for cognitive flexibility to transfer learning skills to novel tasks and attenuating age-related memory impairments.

Disclosures: S.V. Koebele: None. **A.M. Quihuis:** None. **C.N. Lavery:** None. **Z.M.T. Plumley:** None. **H.A. Bimonte-Nelson:** None.

Poster

614. Estrogen Signaling and Cognition

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Program#/Poster#: 614.09/T8

Topic: E.03. Behavioral Neuroendocrinology

Support: NSERC Grant 400212

Title: Role of acetylcholine in the rapid estrogenic facilitation of social learning

Authors: *K. S. ERVIN[1], W. QIU[2], M. SAWULA[2], E. CHOLERIS[2];
[2]Dept. of Psychology and Neurosci. Program, [1]Univ. of Guelph, Guelph, ON, Canada

Abstract: Social learning is a common, adaptive learning strategy in which animals acquire information from conspecifics, avoiding costly trial-and-error individual learning. The social transmission of food preferences (STFP) is a form of social learning in rodents in which an observer prefers a novel food it smelled on the breath of a conspecific demonstrator over other novel foods. Estrogens modulate social learning on this task, both on a long-term/genomic (Clipperton et al,2008,Neuropsychopharmacology,33:2372) and a rapid/non-genomic time scale, specifically through the G protein-coupled estrogen receptor (GPER) (Ervin et al,2015,Psychoneuroendocrinology:doi:10.1016/j.psyneuen.2015.04.002). Consistent with previous literature showing that the STFP is dependent on muscarinic acetylcholine receptor signaling (Boix-Trelis et al,2007,Neurobiol Learn Mem,87:659; Carballo-Márquez et al,2009,Hippocampus,19:446; Carballo-Márquez et al,2009,Neurobiol Learn Mem,91:98), we found that female mice treated IP with the muscarinic antagonist scopolamine were impaired in the STFP. Estrogens increase acetylcholine release in the brain (Mitsushima et al,2009,J Neuroendocrinol,21:400) and GPER is present on cholinergic neurons (Hammond et al,2011,Psychoneuroendocrinology,36:182). Thus estrogens may rapidly facilitate social learning by enhancing acetylcholine release in brain regions important for the STFP. We treated female ovariectomized CD1 mice with 17β-estradiol, the GPER agonist G1, or sesame oil vehicle SC 15min prior to a brief interaction with a previously fed demonstrator, using a protocol with which we previously observed rapid enhancing effects of estrogens on the STFP. 30min prior to estrogen treatment, mice were pretreated IP with either saline vehicle or scopolamine at a subeffective that does not impair social learning on the STFP. If estrogens improve social learning by enhancing muscarinic acetylcholine signaling, scopolamine pretreatment will block the rapid enhancing effect of 17β-estradiol and G1. Little is known about the neural mechanisms underlying social learning, thus our investigations of estrogens' interactions with neurotransmitter systems will greatly contribute to our understanding of this important and ubiquitous learning strategy. Supported by NSERC.

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Poster

614. Estrogen Signaling and Cognition

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Topic: E.03. Behavioral Neuroendocrinology

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NIH Grant AG028084

State of Arizona

ADHS and the Arizona Alzheimer's Disease Core

Title: A comparison of the effects of hormone therapy estrogens, 17β-estradiol and conjugated equine estrogens, on the midbrain serotonin system: Associations between dorsal raphe nucleus tryptophan hydroxylase-2 mRNA levels and cognitive, anxiety-like, and depressive-like behaviors

Authors: *R. HIROI[1,2], G. WEYRICH[1,2], J. S. TALBOOM[3,2], A. JORDAN[1,2], S. V. KOEBELE[1,2], S. MENNENGA[1,2], L. T. HEWITT[1,2], P. MENDOZA[1,2], C. N. LAVERY[1,2], H. A. BIMONTE-NELSON[1,2];
[1]Psychology, Arizona State Univ., Tempe, AZ; [2]Arizona Alzheimer's Consortium, Phoenix, AZ; [3]Banner Sun Hlth. Res. Inst., Sun City, AZ

Abstract: Evidence indicates that decreased serotonin (5-HT) function is associated with a wide range of cognitive and affective disorders. Women, particularly during menopause, are more vulnerable to these disorders than men, and postmenopausal women exhibit decreased serotonergic activity. The serotonergic neurons in the dorsal raphe nucleus (DRN) are a major source of 5-HT in the forebrain. In particular, polymorphisms of tryptophan hydroxylase-2 (TpH2, the brain-specific, rate-limiting enzyme for 5-HT biosynthesis) are implicated in cognitive and affective disorders. Benefits of 17β-estradiol (E2), the most potent naturally circulating estrogen in women and rats, on cognitive, anxiety-like, and depressive-like behaviors have been shown. Moreover, E2 also has been shown to increase TpH2 mRNA in the specific subdivisions of the DRN, and this increase plays a critical role in the regulation of anxiety-like and depressive-like behaviors. Although conjugated equine estrogen (CEE) is a commonly prescribed estrogen component of hormone therapy (HT) in menopausal women, there is a

marked gap in knowledge regarding how CEE affects these behaviors and the brain 5-HT system. Therefore, we evaluated and compared the effects of CEE and E2 treatments on TpH2 mRNA in the midbrain and on behavior. Female rats were ovariectomized, administered either vehicle, E2, or CEE, and tested on a battery of cognitive, anxiety-like, and depressive-like behaviors. The brains of these animals were subsequently analyzed for TpH2 mRNA. The results showed that E2 increased TpH2 mRNA in the caudal and mid subdivisions of the DRN, corroborating previous findings. In contrast, CEE increased TpH2 mRNA in the caudal and rostral, but not the mid DRN, suggesting that distinct estrogens can have subregion-specific effects on TpH2 gene expression. We also found differential correlations between the level TpH2 mRNA in specific DRN subregions and behavior, depending on the type of behavior. These distinct associations imply that regulation of cognition vs anxiety-like vs depressive-like behaviors are modulated by unique serotonergic neurociruitry, opening the possibility of novel avenues of targeted treatment for different types of cognitive and affective disorders.

Disclosures: **R. Hiroi:** None. **G. Weyrich:** None. **J.S. Talboom:** None. **A. Jordan:** None. **S.V. Koebele:** None. **S. Mennenga:** None. **L.T. Hewitt:** None. **P. Mendoza:** None. **C.N. Lavery:** None. **H.A. Bimonte-Nelson:** None.

Poster

614. Estrogen Signaling and Cognition

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Topic: E.03. Behavioral Neuroendocrinology

Support: The University of Wisconsin-Milwaukee, the UWM Research Foundation

NIH R01DA038042

Title: The G-protein-coupled estrogen receptor (GPER/GPR30) modulates cell-signaling proteins that regulate actin polymerization in the dorsal hippocampus of female mice

Authors: *J. KIM, A. M. FORTRESS, K. M. FRICK;
Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: The G-protein coupled estrogen receptor (GPER/GPR30) is a novel membrane estrogen receptor expressed in areas of the brain including the hippocampus. Previously, we demonstrated that a dorsal hippocampal infusion of the GPER agonist G-1 mimicked the effects of 17β-estradiol (E2) on object recognition and spatial memory consolidation in young

ovariectomized female mice. Although our data also suggested that the molecular mechanisms involved in the memory-enhancing effects of GPER differed from those of ERα and ERβ activation, the mechanisms through which GPER regulates memory remain poorly understood. Among several physiological changes underlying memory formation, hippocampal spine remodeling depends on the reorganization of the actin cytoskeleton. Therefore, the present study examined the effects of a dorsal hippocampal infusion of E2 or G-1 on cell-signaling molecules that regulate actin reorganization. Ten week-old ovariectomized C57BL/6 female mice received a bilateral dorsal hippocampal infusion of vehicle, G-1 (4 ng/hemisphere), or E2 (5 µg/ hemisphere), and the dorsal hippocampus was dissected bilaterally 5, 15, or 30 minutes later. Western blot analyses were conducted for proteins including the actin-binding protein cofilin, which depolymerizes actin filaments. G-1 significantly increased phosphorylation of cofilin 5 and 15 minutes after infusion. Because phosphorylation inactivates cofilin, thereby increasing actin polymerization, these data suggest that activation of GPER may increase dendritic spine morphogenesis through actin polymerization. The G-1-induced increase in cofilin phosphorylation was blocked by co-infusion of the selective GPER antagonist G-15, suggesting that GPER activation is necessary for G-1 to regulate cofilin phosphorylation. In contrast, E2 had no effect on cofilin phosphorylation at any of the time points measured. Other cell-signaling molecules involved in actin polymerization are currently being investigated. Collectively, these data provide further support for the conclusion that the molecular mechanisms through which GPER regulates hippocampal function may differ from those of ERα and ERβ.

Disclosures: **J. Kim:** None. **A.M. Fortress:** None. **K.M. Frick:** None.

Poster

614. Estrogen Signaling and Cognition

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 614.12/T11

Topic: E.03. Behavioral Neuroendocrinology

Support: NSERC Grant 400212

Title: A G-protein coupled estrogen receptor agonist in the hippocampus rapidly improves object and social recognition in female mice

Authors: ***J. LYMER**, A. ROBINSON, E. CHOLERIS;
Psychology, Univ. of Guelph, Guelph, ON, Canada

Abstract: Estrogens have been shown to rapidly affect learning and memory in female mice. Specifically, systemic administration of 17β-estradiol, the estrogen receptor (ER) α agonist, PPT, or the G-protein coupled estrogen receptor (GPER) agonist, G-1 rapidly improved social recognition, object recognition, and object placement, while the ER β agonist, DPN improved only social recognition. These paradigms were completed within 40 minutes of drug administration and therefore focus on the rapid, likely non-genomic effects of estrogens. The brain regions involved in mediating these effects are still little understood. The dorsal hippocampus is known to be involved in a number of learning and memory processes and is therefore a good candidate. The research focuses on the role of the GPER specifically in the dorsal hippocampus. G-1 (50, 100, 200nM) was infused (0.5μL/side, 0.2μL/min) directly into the dorsal hippocampus of female mice 15 min prior to testing in social recognition, object recognition, and object placement paradigm. Each mouse was tested in one of the three paradigms, each consisting of two 5min habituations where two stimuli were presented, and one 5 min test phase where one of the stimuli presented was novel and the other was familiar. The social and object recognition paradigms were performed in either the home cage or a Y-apparatus, which has minimal spatial and contextual cues, to help dissociate between the estrogenic facilitation of recognition learning itself, or the facilitation of the use of spatial and contextual cues inherent in the tasks. Dorsal hippocampal activation of the GPER improved social recognition (50nM G-1) and object recognition (200nM G-1) but not object placement in the home cage. Additionally, social recognition (100, 200nM G-1) and object recognition (200nM) were enhanced in the Y-apparatus, where minimal spatial and contextual cues were present. Therefore, the GPER in the dorsal hippocampus appears to be involved in the rapid estrogenic facilitation of social and object recognition, and not necessarily involved in the processing of spatial and contextual information. Supported by NSERC.

Disclosures: **J. Lymer:** None. **A. Robinson:** None. **E. Choleris:** None.

Poster

614. Estrogen Signaling and Cognition

Location: Hall A

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Program#/Poster#: 614.13/T12

Topic: E.03. Behavioral Neuroendocrinology

Support: Louisiana Board of Regents: LEQSF(2013-18)-GF-17

Title: A sex difference in levels of myelin basic protein in the orbitofrontal cortex of adult rats is not impacted by gonadectomy

Authors: *J. DARLING[1], J. M. DANIEL[1,2];
[1]Neurosci. Program, [2]Psychology, Tulane Univ., New Orleans, LA

Abstract: Previous work from our lab revealed that adult female rats have increased levels of myelin basic protein (MBP), a marker of myelination, in the orbitofrontal cortex (OFC) as compared to adult males. However, in prepubertal rats no sex difference in levels of MBP in the OFC is apparent. Therefore, we hypothesized that adult levels of circulating hormones mediate the observed sex difference in MBP levels in adult animals. To test this hypothesis we compared levels of MBP in gonadally intact and gonadectomized adult rats. Male and female adult rats (90d of age) underwent gonadectomies or sham surgeries. Two weeks following surgeries, animals were killed and OFC were dissected and processed for western blotting. Consistent with our previous results, female rats had increased levels of MBP in the OFC than did males. However, there was no impact of gonadal hormone status on levels of MBP. These results indicate that sex differences in levels of MBP in the OFC of adult rats are not due to activational effects of gonadal hormones. Future work will examine the ability of gonadal hormones to act during the perinatal and/or pubertal periods to result in sex differences in adult levels of MBP in the OFC.

Disclosures: J. Darling: None. **J.M. Daniel:** None.

Poster

614. Estrogen Signaling and Cognition

Location: Hall A

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Topic: E.03. Behavioral Neuroendocrinology

Support: University of Wisconsin-Milwaukee College of Letters and Sciences funding to KMF

PSC-CUNY 66720-44 grant to VL

Department of Psychology Summer Research Fellowship to J.J.T

Title: Estradiol-mediated spine changes in the dorsal hippocampus and medial prefrontal cortex depend on ERK and mTOR activation in the dorsal hippocampus of ovariectomized female mice

Authors: *J. J. TUSCHER[1], V. LUINE[2], M. FRANKFURT[3], K. M. FRICK[1];
[1]Psychology Dept., UW-Milwaukee, Milwaukee, WI; [2]Hunter Col. of the City Univ. of New York, New York, NY; [3]Dept. of Sci. Educ., Hofstra North Shore-LIJ Sch. of Med., Hempstead, NY

Abstract: Dendritic spine plasticity is thought to underlie the formation and consolidation of memories. Both natural fluctuations and systemic administration of the sex-steroid hormone 17β-estradiol (E_2) can regulate spine density in the dorsal hippocampus (DH) of rodents. In a previous study, we found that infusion of E_2 directly into the DH also increases dendritic spine density in the DH and medial prefrontal cortex (mPFC). Specifically, E_2 significantly increased basal and apical spine density on CA1 pyramidal neurons 30 minutes after infusion, an effect that persisted for 2 hours. DH E_2 infusion also significantly increased basal spine density on pyramidal neurons in the mPFC by 2 hours after infusion, suggesting that E_2-mediated activity in the DH drives spinogenesis in the mPFC. Previous research has shown DH E_2 infusion enhances hippocampal-dependent object recognition and spatial memory consolidation by rapidly activating ERK-dependent signaling of mammalian target of rapamycin (mTOR), a key protein synthesis pathway involved in spine remodeling. To determine if the E_2-induced spine changes we observed in CA1 and mPFC also depend upon rapid activation of the ERK and mTOR cell-signaling cascades, female mice were infused bilaterally into the DH with vehicle, the ERK inhibitor U0126, or the mTOR inhibitor rapamycin, followed immediately by an intracerebroventricular (ICV) infusion of vehicle or E_2. We found that the increased spine density in CA1 and mPFC observed 2 hours after ICV infusion of E_2 was blocked by DH infusion of the ERK inhibitor U0126 or mTOR inhibitor rapamycin. Collectively, these data suggest that E_2 treatment elicits ERK- and mTOR-dependent spinogenesis on CA1 and mPFC pyramidal neurons, effects which likely support the memory-enhancing effects of E_2 in hippocampus-dependent tasks.

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Poster

614. Estrogen Signaling and Cognition

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 614.15/T14

Topic: E.03. Behavioral Neuroendocrinology

Support: NIH Grant GM060665

Title: Rapid Effects of gonadal hormones on spatial memory and hippocampal spines in male rats

Authors: *V. N. LUINE[1], L. F. JACOME[2], F. LEMA[2], K. BARATELI[2], D. BUITRAGO[2], M. FRANKFURT[3];

[1]Hunter Col., New York, NY; [2]Psychology, Hunter Col. of CUNY, New York, NY; [3]Sci. Educ., Hofstra North Shore-LIJ Sch. of Med., Hempstead, NY

Abstract: Estrogens rapidly enhance hippocampal dependent recognition memory in ovariectomized (OVX) rats by activating cell-signaling cascades, epigenetic processes and dendritic spine density in the hippocampus within 5-30 min of treatment. Whether gonadal hormones elicit similar changes in castrate (CAS) male rats is unknown. Thus, we assessed effects of testosterone (T) and estradiol (E2) on object placement memory and dendritic spine density in the hippocampus. When 750 µg/kg of T was injected immediately after the T1 training trial and retention was tested 2 h later, CAS receiving vehicle spent the same amount of time exploring objects at the old and new locations (3.21 + 0.78 vs 2.72 + 0. 55 sec) whereas T-treated males spent significantly more time exploring at the new location (2.54 + 0.43 vs 5.95 + 1.50 sec, $p < 0.05$). Effects of estrogen were assessed by injecting 20 µg/kg of E2 immediately following the T1 training trial. CAS, vehicle treated males spent the same amount of time exploring objects at the old and new locations (3.91 + 0.15 vs 2.93 + 0.21 sec) whereas E2 treated CAS spent more time exploring at the new location (2.3 + 0.2 vs 5 + 0.05 sec, $p < 0.05$). In a separate experiment, the effects of the hormonal treatments on spine density in the hippocampus were assessed. CAS received vehicle, T or E2 and were sacrificed 30 min or 2 h later, and brains processed for Golgi impregnation using the FD Rapid GolgiStain Kit (Neurotechnologies, Inc). Spines from tertiary apical and secondary basal dendrites in CA1 pyramidal cells and primary dendrites of granule cells in the dentate gyrus (DG) were counted as previously described by the laboratory. After 30 min, a significant increase in CA1 apical spines (ANOVA = $p< 0.003$) was seen with T (40%) and E2 (28%). There were no differences between T and E2, and no effects were present on spines in basal CA1 or DG. Results at two hours post treatment were similar to 30 min, a significant group effect in apical ($p < 0.003$) but not basal CA1 spines with T increasing spine density by 21% and E2 by 31%. No effects were found in the DG. These results show that T and E2 rapidly enhance memory consolidation in the object placement task and cause specific changes in dendritic spine density within the hippocampus, increases in the apical tree of CA1 dendrites in CAS male rats. Effects of E2 are similar to those in OVX rats. In both sexes, E2 did not increase DG spine density. However, in females, basal, but not apical, spines are increased by E2 indicating an anatomical sex difference in CA1. Overall, results show novel gonadal hormonal effects in males and indicate that both sexes respond to gonadal hormones with rapid enhancements in memory and hippocampal spine density.

Disclosures: **V.N. Luine:** None. **L.F. Jacome:** None. **F. Lema:** None. **K. Barateli:** None. **D. Buitrago:** None. **M. Frankfurt:** None.

Poster

614. Estrogen Signaling and Cognition

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Topic: E.03. Behavioral Neuroendocrinology

Support: FWO project G042002

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Hercules Foundation AUHA0012

IAP grant Plastocine P7/17

FWO PostDoc Grant

Title: Rapid and lateralized effects of estrogen manipulation on cognitive auditory processing in a seasonal songbird

Authors: *G. DE GROOF[1], J. BALTHAZART[2], M.-A. CEULEERS[2], C. A. CORNIL[2], A. VAN DER LINDEN[1];
[1]Univ. of Antwerp, Wilrijk, Belgium; [2]Res. Group in Behavioral Neuroendocrinology, Univ. of Liège, Liège, Belgium

Abstract: It has been recently demonstrated that the synthesis or concentration of brain estradiol (E2) is regulated within minutes by neuronal activity in birds [e.g. 1,2]. Recent studies demonstrate the existence of rapid behavioral effects of E2 that are additionally modulated by the photoperiod in mice [3] and by seasons in songbirds [4]. Here, we examined using functional Magnetic Resonance Imaging (fMRI) whether manipulation of E2 rapidly alters auditory processing in the highly social European starling (Sturnus vulgaris) in a season-dependent manner. Adult testosterone-treated male starlings (N=9) were exposed to synthetic pure tones and to two types of male starling song conveying species-specific and individual-specific information [5]. They were imaged twice by fMRI in December (8L:16D; photosensitive), March (11L:13D; late photosensitive) and May/June (16L:8D; photostimulated), a control session immediately followed by a session in which the aromatase inhibitor Vorozole was injected (30mg/kg i.p., 10 min before fMRI). In May/June an extra session was added where E2 (0.5mg/kg i.p.) was injected. Aromatase inhibition differentially affected neural activation elicited by the songs in different seasons. A clear statistically significant effect of Vorozole was detected in the left (but not right) caudal NCM in March but not in December nor May/June. Adding E2 increased neural activation elicited by the stimuli in both left and right NCM. E2 also affected song selectivity (individual-specific vs. species-specific songs), in that they selectively inhibited the neural activation elicited by species-specific songs. The differential response to E2 synthesis inhibition between the different seasons could indicate either a differential aromatase

expression/activity [6] or a change in sensitivity to E2 that would be associated with the increasing photoperiod. T was clamped to stable concentrations during the entire experiment so that the observed changes cannot be attributed to variation in activation by T. Lateralization of the effects of Vorozole on auditory responses in starlings is fascinating and very similar to behavioral findings in zebra finches [7]. Aromatase activity measured *in vitro* in these brains collected one year after the first imaging session (January - photosensitive) was however not different between left and right NCM. The lateralized effect of aromatase inhibition must therefore relate to other steps in estrogen action. 1. Remage-Healey L, et al., (2011). 2. Cornil CA, et al. (2012). 3. Trainor BC, et al. (2008). 4. Heimovics SA, et al. (2015). 5. De Groof G, et al. (2013). 6. Riters LV,. et al. (2001). 7. Remage-Healey L, et al. (2010).

Disclosures: G. De Groof: None. **J. Balthazart:** None. **M. Ceuleers:** None. **C.A. Cornil:** None. **A. Van der Linden:** None.

Poster

614. Estrogen Signaling and Cognition

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 614.17/T16

Topic: E.03. Behavioral Neuroendocrinology

Support: H Lundbeck A/S

Title: Estrogen withdrawal induces depression-like behavior, cognitive dysfunction and temperature dysregulation in a rodent model of perimenopausal symptoms

Authors: *M. GULINELLO[1], C. SANCHEZ[2], Y. LI[2];
[1]Neurosci., Albert Einstein Coll of Med., Bronx, NY; [2]Lundbeck Res. USA, Paramus, NJ

Abstract: Background: The perimenopausal period in human is associated with a range of symptoms including hot flashes, depression and cognitive dysfunction due to the rapid fluctuation of estrogens. Although depression-like behavior has been demonstrated in several rodent models of perimenopause, few of these models have characterized functional changes in more than one relevant behavioral domain. In our current study, we assessed depression-like behavior, cognition and temperature regulation in a rodent model of perimenopausal syndrome that is easy to implement. **Methods**: Female, gonadally intact Sprague Dawley rats were group housed and had ad libitum access to tap water (control) or to water containing 20ug/ml beta-estradiol for 3 weeks (2mg/kg per day) followed by abrupt cessation of estradiol (estrogen withdrawal - EWD). A behavioral test battery was conducted 24-28 hours after EWD and

included the forced swim test and tail temperature measurements (before and after forced swim test) and social memory tests of cognition. Student t-tests were used to analyze the results with $p<0.05$ considered significant. **Results:** Estrogen withdrawal induced depression-like behavior (increased immobility in the forced swim test). During EWD, rats had increased basal tail temperature and slower temperature recovery after the forced swim test, indicating a failure of temperature regulation. Rats undergoing EWD also exhibited impaired social memory. **Conclusion:** Similar to perimenopausal women, estrogen withdrawal in intact rats induced depression-like behavior, temperature dysregulation and memory deficits. This model is feasible to widely implement and would be useful for study the pathophysiology and therapeutic treatments perimenopausal symptoms.

Disclosures: M. Gulinello: None. **C. Sanchez:** None. **Y. Li:** None.

Poster

614. Estrogen Signaling and Cognition

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Topic: E.03. Behavioral Neuroendocrinology

Support: NIH Grant R01AG025340

Title: Physiological arousal enhances memory for negative material in post-menopausal women not on hormone replacement therapy

Authors: *S. E. NIELSEN, M. MATHER;
USC, Los Angeles, CA

Abstract: Few studies have investigated the effect of physiological arousal on memory for emotional material in post-menopausal women, particularly those not on a hormone replacement therapy (HRT) regimen. Our recent work suggests that the effects of arousal on memory are modulated by levels of 17β-estradiol and progesterone in young women (Nielsen, Barber, Chai, and Mather, under review); under arousal, women with lower levels of these sex steroid hormones recalled significantly more negative than positive images. Thus, we tested whether physiological arousal at encoding differentially modulates memory for negative and positive emotional images in post-menopausal women not taking HRT; these older women should have very low levels of sex steroid hormones. Based on our previous work showing the relationship between hormone levels and arousal effects among younger women (Nielsen et al., under review), we predicted that arousal at encoding would enhance short-term emotional memory for

negative images (i.e., high priority images) and suppress memory for positive images (i.e., low priority images). To induce arousal at encoding, some women were administered an isometric handgrip protocol, which has reliably increased endogenous norepinephrine levels in previous studies (see Nielsen et al., under review; Nielsen and Mather, 2015). For the control condition, the handgrip task was replaced with a relaxed water bottle hold. Immediately after, all participants saw a slideshow containing negative, positive, and neutral pictures. Later, all women completed a free recall test for the images. We used eye-tracking technology to assess pupil diameter changes (index of arousal) in response to the handgrip or control task, and we collected salivary samples to assess changes in salivary alpha-amylase (a biomarker for norepinephrine) and levels of 17β-estradiol and progesterone. We tested whether increases in arousal enhanced the tendency to preferentially recall the negative rather than the positive images. A preliminary mixed-model ANOVA revealed a significant two-way interaction between condition (handgrip v. control) and picture valence (negative v. positive) in post-menopausal women ($p < .05$). Follow-up analyses suggest that under arousal, post-menopausal women exhibited an enhanced negativity bias compared to women who completed the control condition ($p < .05$). These preliminary results suggest that physiological arousal at encoding enhances memory for negative, but not positive images, in women as they age and their sex steroid hormone levels substantially decrease.

Disclosures: S.E. Nielsen: None. **M. Mather:** None.

Poster

614. Estrogen Signaling and Cognition

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: E.03. Behavioral Neuroendocrinology

Support: UMSNH Reg. 108907

Title: Anastrozole treatment to ovariectomized rats induces compensatory plastic changes in prefrontal third-layer pyramidal neurons concomitant to working memory impairment

Authors: *D. A. VELÁZQUEZ-ZAMORA[1], N. I. MARTÍNEZ-TORRES[2], M. CERVANTES[3], I. GONZÁLEZ-BURGOS[2];
[1]Univ. Politécnica De La Zona Metropolitana D, Tlajomulco DE Zuniga, Mexico; [2]Inst. Mexicano del seguro Social, Guadalajara, Mexico; [3]Univ. Michoacana de San Nicolás de Hidalgo, Morelia, Mexico

Abstract: Local synthesis of neuroesteroids such as estradiol depends on aromatase activity. Aromatase is expressed in glial cells and neurons in some brain structures such as prefrontal cortex. The prefrontal cortex has a key role in processing the afferent information related with working memory. This executive function is showed to be altered under the absence of estrogenic activity during loss of ovarian function, although the local activity of cerebral-derived estradiol persists. Particularly, both working memory performance and dendritic spines of pyramidal neurons of the layer III of prefrontal cortex are sensitive to the gonadal-proceeding estradiol effects. However, the possible plastic changes in prefrontal dendritic spines underlying working memory performance may be associated with the effects of brain-derived estradiol have not been reported. In the present study, 58 female rats were assigned to four groups: Rats from a control group were ovariectomized bilaterally (Ovx; n=12). Rats from other control were ovariectomized bilaterally, and 1mL of saline solution was administered to each of them (Ovx+Veh; n=12). Another control group of rats were studied in the proestrus stage of their estrous cycle (Proestrus; n=12). An experimental group of rats were ovariectomized bilaterally and treated with 1 mg/kg of Anastrozole in saline solution (Ovx+Ans; n=12). The corresponding pharmacological treatment to Ovx, Ovx+Veh and Ovx+Ans groups was applied at day 6 after ovariectomy. Six animals per group were used for behavioral testing of allocentric working memory in a Y maze. The brains of the remaining six animals per group were used for a morphological study of dendritic spines of layer III pyramidal neurons from prelimbic/infralimbic prefrontal cortex, using a modified version of the Golgi technique. Ovx+Ans group showed less correct responses than all the other groups studied. On the other hand, Ovx+Ans group had less spines than those seen in Proestrus group, but more spines than both Ovx and Ovx+Veh. In addition, only Ovx+Ans group showed filopodial structures. These findings suggest that inhibition of local synthesis of estradiol could be associated with the decreased number of dendritic spines and a compensatory surge of filopodia, as a response to the deficient performance of the working memory task.

Disclosures: **D.A. Velázquez-Zamora:** None. **N.I. Martínez-Torres:** None. **M. Cervantes:** None. **I. González-Burgos:** None.

Poster

614. Estrogen Signaling and Cognition

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Topic: E.03. Behavioral Neuroendocrinology

Support: NIH Grant R01NS050525

Title: Sex differences in neonatal hippocampal neurogenesis impact early life forgetting

Authors: *S. L. STOCKMAN, J. M. BOWERS, M. M. MCCARTHY;
Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Exposure to early life adversity is a major driver of adult health (Felitti et al., Am J Prev Med, 1998). Females are more sensitive to these exposures evident in an increased likelihood to manifest disease, particularly affective-related disorders (Sildberg et al., Arch Gen Psychiatry, 1999). Elevated neurogenesis has been implicated in disruption of established hippocampus-dependent memories causing forgetting (Akers et al. Science, 2014). The magnitude of change in neurogenesis required to shift from learning to forgetting is on par with elevated hippocampal neurogenesis we observe in neonatal males compared to females during the critical neonatal period (Bowers et al., Biol Sex Diff, 2010). Thus we propose elevated neurogenesis in neonatal male hippocampus promotes forgetting of the trauma associated with adverse early life events and diminishes the long-term consequences of such exposure. In order to explore sex differences in early forgetting, we have first demonstrated the ability of neonates to learn utilizing established and novel paradigms. The first paradigm used is an odor-aversion learning assay. In our test, pups are conditioned with odor-footshock pairing on PN6 consisting of a novel vanilla odor with a 1.5mA constant current shock. Testing on PN8 consists of a Y-maze that requires pups to choose between two arms, one containing the vanilla odor and the other with a familiar odor. Learning is evident in aversion to the vanilla odor paired with the aversive stimulus. The second paradigm is a novel learning test we have developed called the Neonatal Learned Aversion (NeoLA) box that employs principles of conditioned place aversion through utilization of pup aversion for cold and bright lights and preference for darkness and warmth. This test utilizes an apparatus divided into a cold and dark side and a warm and bright side. At the start of a trial animals are placed in a hutch on the cold/dark side and given 5 minutes to cross to the warm/bright side. Animals are assisted if they do not cross in 5 min. They are then left on the bright/warm side for 2 min. There are 4 training trials per day from PN4 to PN7. Pups find both the cold and the light aversive but learn to escape the cold with a decreasing latency of 300 seconds down to 89 seconds. Following establishment of learning, assessment of retention at a later time point (PN12) allows for evaluation of forgetting. Investigation of sex differences in neonatal forgetting will provide a basis to understand the contributions of neurogenesis in mediating forgetting of trauma associated with early life adverse event exposure and subsequently understand sex differences in the consequences of such exposure.

Disclosures: S.L. Stockman: None. **J.M. Bowers:** None. **M.M. McCarthy:** None.

Poster

614. Estrogen Signaling and Cognition

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Topic: E.03. Behavioral Neuroendocrinology

Support: Oberlin College Grant-in-Aid

Title: Estradiol and luteinizing hormone affect spatial memory by influencing cell proliferation and expression of brain-derived neurotrophic factor

Authors: N. BOHM-LEVINE, A. GOLDBERG, E. VARRONE, *J. E. THORNTON; Neurosci. Dept, Oberlin Col., Oberlin, OH

Abstract: In humans, both ovariectomy and menopause are associated with memory loss. Concomitant with this, there is a substantial drop in estradiol (E) and a large increase in luteinizing hormone (LH) due to decreased negative feedback by E. Ovariectomized (ovx) female rats also exhibit deficits in various forms of spatial memory and either raising E or lowering LH levels reverses these memory deficits (e.g. Berry et al., 2008; Ziegler and Thornton, 2010). Estradiol has been shown to increase neurogenesis and expression of neurotrophic factors in the hippocampus, which may account for estradiol's mnemonic benefits (Barker and Galea, 2008; Solum and Handa, 2002). The present studies investigated whether LH decreases hippocampal cell proliferation and/or brain-derived neurotrophic factor (BDNF) levels. Female Sprague-Dawley rats were ovx and implanted with either an E or blank (blk) capsule. Animals were injected with the LH homologue hCG (human chorionic gonadotropin), Antide (a gonadotropin releasing hormone receptor antagonist that decreases LH levels) or vehicle (0.9% saline), and brains were collected 4-6 hours later. Tissue was processed using immunohistochemistry and examined for cells expressing Ki67, a nuclear protein present during mitosis, and for BDNF. E treatment significantly increased the number of Ki67-immunoreactive cells in the dentate gyrus compared to controls (ovx + E vs. ovx + blk); however, decreasing LH with Antide treatment had no clear effect on cell proliferation (ovx + Antide vs. ovx + blk). In contrast, both E and Antide treatment significantly increased BDNF levels in the dorsal hippocampus of ovx rats (ovx + E and ovx + Antide vs. ovx + blk). To further investigate whether the hormone-mediated mnemonic improvements are dependent on BDNF, ovx + E animals were injected with the BDNF TrkB receptor antagonist ANA-12 (0.5mg/kg, Sigma) or vehicle, 4-6 hours prior to behavioral testing on the Object Location Test (OLT). Consistent with previous results, ovx + E animals displayed improved spatial memory compared to ovx + blk. Conversely, ANA-12 treatment led to a loss of spatial memory in ovx + E animals, indicating an important role for BDNF in E-induced memory recovery. Future studies will determine whether ANA-12 treatment similarly attenuates Antide's effects on spatial memory in ovx rats.

Disclosures: N. Bohm-Levine: None. **A. Goldberg:** None. **E. Varrone:** None. **J.E. Thornton:** None.

Poster

614. Estrogen Signaling and Cognition

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Topic: E.03. Behavioral Neuroendocrinology

Support: NIH Grant NS042767 (CJS)

Title: Hippocampal aromatization modulates spatial memory in the zebra finch via the action of estradiol on membrane receptors

Authors: *D. J. BAILEY[1], E. R. PAITEL[2], J. A. GUNDERSON[1], Y. V. MAKEYEVA[1], C. J. SALDANHA[3];
[1]Biol., [2]Psychology, St. Norbert Col., De Pere, WI; [3]Biol., American Univ., Washington, DC

Abstract: Synaptic aromatization has recently emerged as an intensely studied aspect of neuroendocrine function. Aromatase expression in the adult zebra finch hippocampus (HP) is among the highest compared to other neural loci and is localized primarily pre- and postsynaptically. Previously we established that application of an aromatase inhibitor to the male zebra finch HP increased the number of learning trials in a spatial memory task and the mistakes made during/time to complete the probe trials. Notably, these birds performed indiscernibly from those with HP lesions. While these data suggest that synaptic estradiol (E2) may be important in HP-dependent memory function, studies involving (1) concurrent replacement of this steroid in birds treated with an aromatase inhibitor and (2) the role of estrogen receptors, particularly the G protein-coupled estrogen receptor (GPER) implicated in rapid E2 signaling, are necessary to test this hypothesis. Adult male zebra finches were anesthetized and received a bilateral craniotomy above the HP. Birds were given one of the following manipulations: silicone pellets (SIL) or identical pellets soaked with the aromatase inhibitor ATD (1,4,6-androstatriene-3,17-dione), ATD+E2, the GPER agonist G-1 or the antagonist G-15. Three days later, birds were food-deprived and tested for acquisition and retention of a food location. ATD-treated birds took significantly more trials to reach criterion relative to SIL birds, but the performance of ATD+E2 birds was statistically indistinguishable from both SIL and ATD birds. While application of G-1 to the HP did not significantly affect acquisition relative to SIL birds, all G-15 birds were unable to reach the predetermined criterion level. During probe trials 1 hr following acquisition, ATD birds took the longest to reach the baited cup and made more mistakes relative to the other groups. Interestingly, ATD+E2 animals displayed the lowest overall retention latencies and made significantly fewer mistakes than birds treated with ATD. Thus, spatial memory acquisition and performance appear aromatase dependent, while its E2 dependence is more reliably revealed

following consolidation and/or during recall. This study provides evidence that (1) the decrease in spatial memory performance of ATD-treated birds likely reflects a specific effect on synaptic E2 synthesis and (2) this effect is at least in part mediated by GPERs. Additional studies on tissue collected from these birds will begin to determine the signal transduction systems mediated by synaptic E2 provision and necessary for HP-dependent memory function.

Disclosures: D.J. Bailey: None. **E.R. Paitel:** None. **J.A. Gunderson:** None. **Y.V. Makeyeva:** None. **C.J. Saldanha:** None.

Poster

614. Estrogen Signaling and Cognition

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 614.23/U2

Topic: E.03. Behavioral Neuroendocrinology

Support: NIA R01AG032325

Title: Luteinizing hormone receptor activation in the CNS increases neurite outgrowth and spatial memory

Authors: *J. A. BLAIR[1], H. MCGEE[2], X. WANG[3], G. CASADESUS SMITH[2,1];
[1]Biomed. Sci., [2]Biol. Sci., Kent State Univ., Kent, OH; [3]Pathology, Case Western Reserve Univ., Cleveland, OH

Abstract: Elevated peripheral levels of luteinizing hormone (LH) have been linked to deficits in spatial memory and reductions in dendritic spine density *in vivo*. An inverse relationship exists such that pharmacologically reducing levels of LH in the periphery results in its increase in the CNS, thus improving cognitive performance. Therefore, we hypothesized that increases in LH receptor (LHR) signaling in CNS ameliorates learning and memory as well as improves neuronal morphology. To test our hypothesis, we delivered an LH analogue (hCG) into the lateral ventricles of young female mice with an ovariectomy-induced decrease in CNS LH levels. Our preliminary data suggest that LH rescues ovariectomy associated deficits in spatial memory in Morris water maze. To elucidate LHR action *in vitro* we treated primary hippocampal neurons with hCG, which resulted in an increased number of secondary neurites and branch points. In conclusion, our work shows that central delivery of LH improves learning and memory as well as dendritic arborization, suggesting that increased LHR signaling in the CNS will ameliorate cognitive function in aging females.

Disclosures: **J.A. Blair:** None. **H. McGee:** None. **X. Wang:** None. **G. Casadesus Smith:** None.

Poster

614. Estrogen Signaling and Cognition

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 614.24/U3

Topic: E.03. Behavioral Neuroendocrinology

Support: Harris Research Endowment, Drake University

Title: Does maternal genistein impair non-spatial, hippocampal-dependent memory in adulthood?

Authors: *C. C. WRENN, C. T. LANGRECK, S. A. LOTHSPEICH;
Coll Pharm. & Hlth. Sci., Drake Univ., Des Moines, IA

Abstract: The soy-derived phytoestrogen genistein has received interest as an endocrine disruptor due to its ability to bind estradiol receptors. Among the functions that may be impacted by endocrine disruptors are learning and memory. Previous work from our laboratory has shown that exposure of male rats to genistein through the maternal diet results in impaired learning in the water maze, a hippocampal-dependent spatial task. In the current study we tested the hypothesis that maternal exposure to genistein also impairs learning in a hippocampal-dependent non-spatial task, the social transmission of food preference (STFP). STFP is an olfactory task in which rats use their memory for a socially presented scent cue to guide food choice. We exposed male rats to genistein by allowing pregnant dams to consume food containing the phytoestrogen (5 mg/kg) throughout gestation and lactation. After weaning, we placed male rats on a phytoestrogen-free diet and tested them in STFP at approximately 2-3 months of age. Control and genistein-exposed rats did not differ in their ability to use memory for a scent to guide food choice. These data suggest that genistein-exposure during development does not cause an impairment in a non-spatial hippocampal task. Future work will assess the effect of maternal genistein exposure on other hippocampal tasks such as trace fear conditioning.

Disclosures: **C.C. Wrenn:** None. **C.T. Langreck:** None. **S.A. Lothspeich:** None.

Poster

614. Estrogen Signaling and Cognition

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 614.25/U4

Topic: B.08. Synaptic Plasticity

Support: Psychiatric Research Trust

Medical Research Council (MRC) UK

Royal Society UK

Brain and Behavior Foundation (formally National Alliance for Research on Schizophrenia and Depression (NARSAD))

Title: Estrogen sensitive G-protein coupled receptor (GPER1) rapidly regulates dendritic spine turnover and PSD-95 dynamics

Authors: *K. SELLERS[1], P. RAVAL[1], I. A. WATSON[1], T. Z. DEEB[2], J. MUKHERJEE[2], F. ERLI[3], D. GADD[1], N. J. BRANDON[4,2], D. P. SRIVASTAVA[1];
[1]Dept. of basic and clinical neuroscience, Kings Col. London, London, United Kingdom; [2]AstraZeneca-Tufts Lab. for Basic and Translational Neurosci., Tufts Univ. Med. Sch., Boston, MA; [3]Dept. of Biotech. and Biosci., Univ. of Milano-Bicocca, Milan, Italy; [4]AstraZeneca Neurosci. IMED, Cambridge, MA

Abstract: In the mammalian forebrain, the majority of excitatory synapses form on dendritic spines. Changes in the number of dendritic spines are important for brain development, plasticity and the refinement of neural circuits. In addition, alterations in dendritic spine number occur during the acquisition of learned behaviours, suggesting an intimate relationship between the regulation of these post-synaptic structures and cognitive function. Multiple studies have demonstrated that the 17β-estradiol (E2), the major biologically active form can modulate cognition within a rapid time frame. In addition to this there is increasing body of evidence to suggest that E2 is capable of rapidly activating a number of signalling cascades resulting in alteration of dendritic spines, consistent with its effects on cognition. While these effects have been attributed in the main to signalling via the estrogen receptors (ER) ERα and ERβ, recent studies have suggested that the recently identified E2 sensitive receptor, G-protein coupled estrogen receptor 1 (GPER1), may also mediate E2-dependent modulation of cognition. However, whether signalling via GPER1 can also mediate spine-morphogenic responses are not clear. Here we report using superresolution microscopy that GPER1 is present at a subset of synapses in excitatory cortical neurons where it forms nanodomains with PSD-95. We demonstrate that signalling through GPER1 results in the activation of distinct signalling cascades in primary cortical neurons. Time-lapse imaging demonstrates that pharmacological

activation of GPER1 results in an increase in dendritic spine turnover and motility, and an increase in spine linear density. Moreover, GPER1-medaited spinogenesis is dependent on its C-terminal, a domain essential for its synaptic localisation and interaction with synaptic proteins including PSD-95. In addition, we observe an increase in PSD-95 trafficking, resulting in its localisation in newly formed spines. Activation of GPER1 also resulted in altered synaptic expression of AMPA-receptors and AMPA-receptor mediated transmission. These findings suggest that in cortical neurons, E2 signalling via GPER1, is capable of remodelling neuronal circuits by increasing the number of excitatory synapses.

Disclosures: **K. Sellers:** None. **P. Raval:** None. **I.A. Watson:** None. **T.Z. Deeb:** None. **J. Mukherjee:** None. **F. Erli:** None. **D. Gadd:** None. **N.J. Brandon:** None. **D.P. Srivastava:** None.

Poster

614. Estrogen Signaling and Cognition

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 614.26/U5

Topic: B.08. Synaptic Plasticity

Support: Medical Research Council (MRC) UK Grant MR/L021064/1

Royal Society UK Grant RG130856

Brain and Behavior Foundation Grant 18087

Title: Local activation of Ras-like small GTPase Rap1 is required for estrogen-induced spine formation

Authors: *D. P. SRIVASTAVA[1], A. SHUM[2];
[1]Inst. of Psychiatry, Psychology and Neuroscien, London, United Kingdom; [2]Northwestern Univ., Chicago, IL

Abstract: There is a growing appreciation that estrogens, in particular, 17β-estradiol (estradiol) exert a positive effect on cognitive function within a rapid time frame (minutes to hours). These cognitive enhancing effects have been shown to be dependent on the activation of specific signalling pathways and are accompanied by increases in spine density in several areas of the brain. Recent studies have now begun to link the activation of specific signalling pathways with estradiol-induced spine plasticity. Interestingly, the initial formation of dendritic spines by estradiol is independent of protein synthesis and gene transcription, and thus, wholly reliant on

the activation of cytosolic signalling pathways. However, the direct observation of estradiol-induced signalling in dendrites or in dendritic spines has not been shown. The Ras-family of small GTPases, which includes Rap1, play important roles in the morphogenesis of dendritic spines. We have previously shown that a Rap1-dependent pathway is critical for estradiol-induced spine formation in cortical neurons. Using a unimolecular FRET-sensor for Rap1, we have monitored the spatiotemporal dynamics of Rap1 activation in live cortical neurons following treatment with estradiol. In distal dendrites and dendritic spines, we observe a highly compartmentalized activation of Rap1 following estradiol treatment. This is maximal within 30 minutes, consistent with estradiol's effects on dendritic spine density. Remarkably, we find that active Rap1 accumulates within dendrites directly below and preceding the formation of a nascent dendritic spine. Subsequently, activate Rap1 diffuses into the newly formed spine, suggesting that Rap1 is play a role in co-ordinating the formation of a nascent spine. Importantly, overexpression of a dominant-negative Rap1 mutant (Rap1 N17) blocks estradiol-induced spine formation. These data demonstrate that estradiol specifically activates a Rap-dependent pathway locally within dendrites and dendritic spines, which co-ordinate the formation of nascent dendritic spines.

Disclosures: D.P. Srivastava: None. **A. Shum:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.01/U6

Topic: E.05. Stress and the Brain

Support: NIH MH62044

Title: The effect of sex and social status on gene expression in Syrian hamster brain

Authors: *K. E. MCCANN, D. M. SINKIEWICZ, A. NORVELLE, K. L. HUHMAN; Neurosci. Institute, Ctr. for Behavioral Neurosci., Georgia State Univ., Atlanta, GA

Abstract: Male and female Syrian hamsters are highly territorial and are readily aggressive towards an intruding conspecific. After losing one agonistic encounter, however, hamsters abandon all territorial aggression and, instead, become highly submissive. This change in behavior has been termed conditioned defeat. While both males and females exhibit conditioned defeat, the behavioral expression varies and is overall more pronounced in males. To investigate potential molecular mechanisms leading to sexually dimorphic expression of conditioned defeat,

we used transcriptomic analysis. First, we sequenced the entire brain transcriptome of male and female hamsters and compared baseline expression levels. Using a false discovery rate of <0.001 and a log2 fold change of >1 or <-1, we found 306 differentially expressed genes, 232 of which were up regulated in females compared with males. Next, we sequenced transcriptomes of basolateral amygdalae taken from dominant and subordinate animals and compared these with amygdalae from home cage controls. The basolateral amygdala is necessary for both acquisition and expression of conditioned defeat, and thus we sought to investigate differential gene expression in this nucleus of males and females of different social status. In males, expression of 37 genes decreased and 10 genes increased in both subordinate and dominant animals compared with socially isolated controls. Interestingly, 14 genes showed directional opposition (i.e., 8 increased in dominants while decreasing in subordinates; 6 increased in subordinates that decreased in dominants). Ultimately, 10 unique genes were specifically up-regulated in subordinate, and 12 unique genes were specifically up-regulated in dominant males. A similar pattern emerged in females. Expression decreased in 26 genes and increased in 16 genes in dominant and subordinate animals compared with controls. Only 6 genes showed directional opposition in females (2 genes increased in dominants that decreased in subordinates, and 4 genes increased in subordinates that decreased in dominants). Overall, 11 unique genes were specifically up-regulated in subordinate females and 10 were specifically up-regulated in dominant females. We are currently analyzing these data to determine if the genes that are differentially expressed are similar between males and females and to establish what role, if any, these genes play in the behavioral changes observed following agonistic experience. Supported by NIMH award R01MH062044 to KLH. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Disclosures: **K.E. McCann:** None. **D.M. Sinkiewicz:** None. **A. Norvelle:** None. **K.L. Huhman:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.02/U7

Topic: E.05. Stress and the Brain

Support: NIH Grant R01MH062044

Title: Brain derived neurotrophic factor in the medial prefrontal cortex reduces the acquisition of conditioned defeat

Authors: *A. M. ROSENHAUER, B. M. THOMPSON, T. E. LARKIN, K. L. HUHMAN; Neurosci. Inst., Georgia State Univ., Atlanta, GA

Abstract: Syrian hamsters readily display aggressive behaviors to defend their territories under laboratory conditions and thus are ideal for the ethologically relevant study of the effects of social stress on brain and behavior. Hamsters also show a striking failure to exhibit their normal territorial aggression after a single pairing with a larger, more aggressive conspecific that results in social defeat. This behavioral change has been termed conditioned defeat (CD) and is exhibited by animals even when they are subsequently paired with a smaller, non-aggressive intruder (NAI) in the defenders' home cages. Our lab has worked to delineate the neural circuit and the neurochemical signals that mediate CD. We have shown that, similar to classical fear conditioning, CD is dependent on neural activity in the basolateral amygdala (BLA) and the medial prefrontal cortex (mPFC). Surprisingly, we have also shown that peripherally administered brain-derived neurotrophic factor (BDNF) TrkB receptor agonists, which are known to promote learning and memory, unexpectedly reduce the acquisition and consolidation of CD. As it is known that the mPFC can inhibit fear learning by its downstream effects on the BLA, a critical node in the neural circuit mediating CD, it is possible that the peripherally administered BDNF-active drugs inhibited CD via their action in the mPFC. The purpose of this experiment was to test this possibility. Thus, BDNF (0.4 ng in 200 nl saline) was administered into the medial pre-frontal cortex prior to a 15-minute defeat training session. Hamsters were then tested 24 hr later with a NAI. Hamsters microinjected with BDNF displayed significantly less submissive behavior than did vehicle controls during testing indicating that BDNF in the mPFC decreases the acquisition of CD. We are now beginning to explore whether BDNF has different effects on CD acquisition depending on what subregion (i.e., prelimbic versus infralimbic) of the mPFC is targeted. Supported by NIMH award R01MH062044 to KLH. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Disclosures: A.M. Rosenhauer: None. **B.M. Thompson:** None. **T.E. Larkin:** None. **K.L. Huhman:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.03/U8

Topic: E.05. Stress and the Brain

Support: NIMH Grant R01MH062044

Title: Brain derived neurotrophic factor impairs consolidation of conditioned defeat learning but does not impair learning of social cues

Authors: *K. A. PARTRICK, B. M. THOMPSON, T. E. LARKIN, Z. SONG, K. L. HUHMAN;
Neurosci. Inst., Atlanta, GA

Abstract: Syrian hamsters are territorial animals that attack intruders. After a brief social defeat, however, hamsters no longer display territorial aggression, even when paired with a smaller, non-aggressive intruder (NAI). Instead, defeated hamsters display submissive behavior, and this response has been termed conditioned defeat (CD). Brain derived neurotrophic factor (BDNF) and its receptor TrkB are known to mediate fear learning and are prevalent in brain regions known to be important for CD. Surprisingly, our lab has previously shown that TrKB receptor agonists administered centrally or peripherally decrease the consolidation of CD, while a TrkB receptor antagonist administered peripherally enhances CD. Therefore, it appears that BDNF may impair fear leaning following social defeat. Alternatively, it is possible that BDNF improves learning of cues associated with the original defeat so that hamsters display a reduced generalization when paired with an NAI. The purpose of this experiment was to test whether the TrkB receptor agonist 7,8-dihydroxyflavone (7,8-DHF; 10 mg/kg ip) alters learning of social cues. Hamsters were exposed to the flank gland secretion of a conspecific on a glass slide (3min) on Day 1. Immediately after the scent exposure, hamsters were injected with 7,8-DHF or vehicle. On Day 2, hamsters were re-exposed to a slide with scent from the familiar opponent as well as a second slide with flank secretions from a novel conspecific. Time (s) spent sniffing each scent during a 3min trial was recorded. In general, hamsters spend more time during the second test sniffing the novel scent, demonstrating that they are capable of social recognition 24 after scent exposure. Hamsters given 7,8-DHF exhibited neither enhancement nor impairment of social learning. Equal numbers of animals (i.e., 8 of 10) in each group preferred the unfamiliar scent during testing, demonstrating similar social recognition between groups. These data suggest that our previous finding that 7,8-DHF reduces conditioned defeat is not due to a non-specific effect of 7,8-DHF on learning of social cues. Instead, it appears that BDNF may promote resilience to social defeat in hamsters. Supported by NIMH award R01MH062044 to KLH. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Disclosures: **K.A. Partrick:** None. **B.M. Thompson:** None. **T.E. Larkin:** None. **Z. Song:** None. **K.L. Huhman:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.04/U9

Topic: F.02. Animal Cognition and Behavior

Support: Fondo incentivos Universidad de Costa Rica

Title: Effects of environmental enrichment and social isolation and the reversion of those conditions on anxiety and fear conditioning

Authors: *A. MORA-GALLEGOS, S. SALAS, J. FORNAGUERA;
Univ. of Costa Rica, San Jose, Costa Rica

Abstract: Environmental enrichment (EE) and social isolation (SI) have lasting effects on brain and behavioral parameters including emotions such as fear and anxiety. We focused on differences between EE and SI rats and on the possible effects produced by the reversion of those conditions on fear and anxiety. We measured anxiety (Open Field Test-OFT and Plus Maze-PM), fear (Fear Conditioning-FC) and levels of DOPAC (DA) and dopamine (DA) on prefrontal cortex (PFC), and amygdala (AMY) using HPLC-EC. In experiment 1, anxiety tests were carried out before, one and two months after starting housing conditions. FC procedure was conducted after two months of housing. After behavioral tests, animals were sacrificed for neurochemical analysis. In experiment 2, housing conditions were reverted (EE to SI and SI to EE), and maintained also for two months, keeping their respective control groups. Anxiety tests were done as in experiment 1 and fear to the context (FCC) was conducted at the end of housing. Sacrifices were conducted as in experiment 1. In experiment 1 EE rats were less reactive on anxiety tests and FC. Anxiety effects are reflected mainly in OFT locomotion and exploration but also in PM behaviors. In FC procedure, EE rats showed higher levels of freezing. EE rats showed higher DA turnover in PFC and in AMY than SI rats (not significant). In experiment 2, in OFT and PM, EE showed less anxiety behaviors than SI similar to experiment 1. For reversion conditions we found that SI-EE behaviors are more alike to EE and that EE-SI behaviors are more alike to SI, after two months of the reversion. Reverted conditions didn´t show differences in FCC. For neurochemistry, although there were no significance, EE rats showed higher DA turnover on PFC and AMY than SI rats, and reverted conditions seem to decrease when compared to their original housing conditions. Taken together, our results confirm that EE rats have better strategies to cope with anxiety and fear, and these effects at behavioral and neurochemical levels are maintained at two and four months of housing. Additionally, reversion of housing conditions can modify animals' behaviors and DA turnover in the PFC and AMY.

Disclosures: **A. Mora-Gallegos:** None. **S. Salas:** None. **J. Fornaguera:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.05/U10

Topic: F.02. Animal Cognition and Behavior

Title: Effects of differential housing on emotional behaviors and expression of BDNF and CRF in hippocampus and amygdala

Authors: *S. SALAS, A. SEQUEIRA, J. FORNAGUERA, A. MORA-GALLEGOS;
Univ. of Costa Rica, San José, Costa Rica

Abstract: Fear and anxiety are central for the understanding of many psychological disorders and neurodegenerative diseases.These emotions seem to be modulated by the environment in which the subject develops. To study the effect of rearing environments on fear and anxiety,we used differential housing conditions during 2 months (social isolation, standard control and environmental enrichment) on male Sprague-Dawley rats and tested different behavioral parameters in the open field test, plus maze test and fear conditioning paradigm. One week after the last testing session, animals were sacrificed in order to analyze the expression of BDNF and CRF in the hippocampus and amygdala, by means of RT-qPCR. Social isolated rats showed anxious behavioral patterns in the open field test, while enriched rats seem to be less reactive to the new environment. In the plus maze test, analysis of time spent in open and close arms did not show housing effects, but other behaviors like stretched-attended posture, head dipping, rearing and grooming did, showing consistence with the open field test results. There were also performance differences on fear conditioning task; enriched animals showed higher levels of freezing than the other two groups. This behavior has been classically associated with more efficient emotional memory. In regard to the expression analysis, enriched animals showed higher levels of BDNF in the hippocampus than the other two groups, while control animals had higher levels of BDNF in the amygdala, as well as CRF in both regions. Our results suggest that environmental enrichment has an effect primarily on hippocampal BDNF, region related to memory and spatial information processing. In the amygdala, the similarities showed between enriched and isolated animals, could be explained by a more generalized coping mechanism for emotional challenges.Even though the enriched group showed better performance in the behavioral tests, there seem to be some coincidence in regulatory mechanisms of gene expression in both hippocampus and amygdala.

Disclosures: S. Salas: None. **A. Sequeira:** None. **J. Fornaguera:** None. **A. Mora-Gallegos:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.06/U11

Topic: E.05. Stress and the Brain

Support: NIH Grant MH098190

Title: Cellular mechanisms by which social status alters behavioral responses to stress

Authors: S. SEDDIGHI, A. K. BARNES, C. T. CLINARD, *M. A. COOPER;
Dept. of Psychology, Univ. of Tennessee, Knoxville, TN

Abstract: Understanding the cellular mechanisms that control resistance and vulnerability to stress is an important step toward identifying novel targets for the prevention and treatment of stress-related mental illness. Dominant and subordinate animals have been shown to exhibit different behavioral and physiological responses to stress, with dominants often showing stress resistance and subordinates showing stress vulnerability. We have previously found that dominant hamsters exhibit reduced social avoidance following social defeat stress compared to subordinate hamsters, although the extent to which stress resistance in dominants generalizes to non-social stressors is unknown. In this study dominant, subordinate, and control male Syrian hamsters were exposed to acute restraint stress for 30 minutes. In one cohort of animals, brains were collected for c-Fos immunohistochemistry following restraint stress. In a second cohort, blood samples were collected immediately following restraint and animals were tested for anxiety-like behavior in an open field arena 24 hours later. Preliminary data indicate that restrained animals exhibited increased plasma cortisol compared to non-restrained controls. Also, restraint stress increased the number of c-Fos-positive cells in several brain regions including the infralimbic cortex, prelimbic cortex, medial amygdala, and paraventricular nucleus of the hypothalamus. Analysis of c-Fos immunoreactivity, plasma cortisol, and anxiety-like behavior in dominant and subordinate animals is ongoing. This project will address whether resistance to social defeat stress in dominant hamsters generalizes to restraint stress and extend existing literature on the domain-general vs. domain-specific nature of stress resilience.

Disclosures: S. Seddighi: None. **A.K. Barnes:** None. **C.T. Clinard:** None. **M.A. Cooper:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.07/U12

Topic: E.05. Stress and the Brain

Support: NIH R21 MH098190

NARSAD Grant 19260

Title: Metabolomics of Resilience to Social Stress

Authors: *B. N. DULKA[1], A. K. BOURDON[2], C. T. CLINARD[1], M. B. MUVVALA[3], S. R. CAMPAGNA[2], M. A. COOPER[1];
[1]Psychology, [2]Chem., [3]Univ. of Tennessee, Knoxville, TN

Abstract: Social defeat represents a naturalistic form of conditioned fear and is an excellent model in which to investigate the biological basis of stress resilience. While there is growing interest in identifying biomarkers of resilience, until recently it has not been feasible to associate levels of multiple neurochemicals in several brain regions to stress-related phenotypes. Metabolomics is a quantitative analysis of small molecules present in biological systems and has been increasingly used for the discovery of biomarkers. The objective of the present study was to identify neurochemicals in select brain regions that distinguish susceptible and resilient individuals in two rodent models of acute social defeat: one with mice and another with Syrian hamsters. We expect that this comparative approach will add strength to the generalizability of these findings. In the first experiment, male mice were subjected to acute social defeat stress using a resident-intruder model and tested for social avoidance 24 hours later in an open field arena to phenotype individuals as resilient or susceptible. One week later, mice were subjected to a second acute social defeat episode, and tissue was immediately collected from the medial prefrontal cortex (mPFC), amygdala (AMY), nucleus accumbens (NAC), and hippocampus (HPC). Liquid chromatography coupled with both tandem and high resolution mass spectrometry (LC-MS) was then used for neurochemical and metabolite detection. In the second experiment, we paired male Syrian hamsters in daily agonistic encounters for 2 weeks, during which they formed stable dominant-subordinate relationships. Then, 24 hours after the last pairing animals were exposed to acute social defeat stress. Immediately after social defeat tissue was collected from the mPFC, AMY, NAC, and HPC, and each sample was analyzed using LS-MS. Preliminary analyses indicate several small molecules that significantly differ between defeated and non-defeated animals. For example, defeated hamsters exhibited higher levels of DOPAC in the HPC and AMY and lower levels of NAD+/NADH in the AMY, HPC, and mPFC compared to home cage controls, suggesting increased metabolism of dopamine and impaired energy

metabolism, respectively. Analyses to identify metabolites that distinguish susceptible and resilient animals are ongoing. We believe that taking a metabolomics approach is an essential first step toward developing novel biomarkers for stress-related mental illness.

Disclosures: B.N. Dulka: None. **A.K. Bourdon:** None. **C.T. Clinard:** None. **M.B. Muvvala:** None. **S.R. Campagna:** None. **M.A. Cooper:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.08/U13

Topic: E.05. Stress and the Brain

Support: NIH Grant R21 MH098190

Title: The role of androgen receptor signaling in the maintenance of dominance status and resistance to conditioned defeat

Authors: *C. T. CLINARD, S. G. ADLER, M. A. COOPER;
Psychology, Univ. of Tennessee, Knoxville, TN

Abstract: Winning aggressive disputes is one of several experiences that can alter responses to future stressful events. We have previously tested dominant and subordinate male Syrian hamsters (Mesocricetus auratus) in a conditioned defeat model and found that dominant individuals show reduced defeat-induced changes in behavior compared to subordinates. Also, resistance to the effects of social defeat in dominants is experience-dependent and requires 14 days of dominance encounters to develop. Testosterone is a potential neuroendocrine signal regulating differences in how dominants and subordinates respond to stress because winning aggressive encounters can increase plasma testosterone and androgen receptor expression in select brain regions. Our objective was to determine whether a surge in testosterone after winning aggressive interactions modulates the experience-dependent neural plasticity supporting stress resiliency. In the first experiment, male hamsters were paired in 10-min aggressive encounters and blood samples were collected immediately before and 15-min after agonistic interactions. Dominants showed a significant rise in plasma testosterone compared to their baseline hormone measurement, whereas subordinates and control animals showed no change in testosterone. The second experiment investigated whether changes in androgen receptor immunoreactivity occur during the maintenance of dominance relationships. We paired male hamsters in daily agonistic encounters for 14 days to establish and maintain

dominant/subordinate relationships, and then collected brain tissue for androgen receptor immunohistochemistry. Dominant animals showed significantly more cells expressing androgen receptor immunoreactivity, compared to subordinates and controls. In the third experiment, we are currently investigating if this androgen receptor-dependent signaling is necessary during the maintenance of dominance status for resistance to conditioned defeat. These results suggest that daily surges in plasma testosterone during the maintenance of dominance status coincide with the development of conditioned defeat resistance, and that testosterone is a potential neuroendocrine signal modulating experience-dependent neural plasticity controlling resistance to conditioned defeat in dominant hamsters.

Disclosures: C.T. Clinard: None. **S.G. Adler:** None. **M.A. Cooper:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.09/U14

Topic: E.05. Stress and the Brain

Support: HDRF Grant RGA13-004

NIH Grant MH102065

NIH Grant MH41256

Title: Sex-specific gene expression changes in CA3 neurons of heterozygous BDNF Val66Met mice mimics some effects of acute stress

Authors: *J. MARROCCO[1], M. B. RÍOS[1], J. F. KOGAN[1], J. D. GRAY[1], E. M. WATERS[1], E. F. SCHMIDT[2], N. HEINTZ[2], B. S. MCEWEN[1];
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Abstract: Stress is a precipitating factor for neuropsychiatric disorders, such as anxiety and depression. Preclinical and clinical evidence suggest that stress effects on the brain and the ensuing behavioral responses differ between the sexes. Gene expression and epigenetic studies are helping to unravel the molecular underpinnings of such sex differences. Brain-derived neurotrophic factor (BDNF) has been postulated to lay at the core of the stress-response in the hippocampus, a brain region implicated in mood disorders, and a common single-nucleotide polymorphism in the human BDNF gene (Val66Met) has been associated with increased vulnerability to depression. Here we hypothesized that mice heterozygous for the Met allele

would exhibit gene expression changes similar to stressed mice even without applied stressors. We used double transgenic mice bearing both a heterozygous variant $BDNF_{Met}$ knock-in and a Bacterial Artificial Chromosome (Bac) in which the EGFP-L10a is selectively expressed in the vulnerable CA3 region. Genetically-targeted translating ribosome affinity purification (TRAP) and RNA-Seq analysis revealed that about 76% of the total entities analyzed were affected similarly in acutely stressed (FST, forced-swim test) $BDNF^{+/+}$ females and in unstressed $BDNF^{+/Met}$ females. Interestingly, $BDNF^{+/Met}$ males did not exhibit the same profile when compared to FST $BDNF^{+/+}$ males and both differed with respect to sex. One marker of acute stress, c-Fos, was only increased in FST $BDNF^{+/+}$ males and females, indicating that $BDNF^{+/Met}$ mice had not activated the immediate early gene transcription cascade. Yet, we found that genes that were simultaneously upregulated in FST $BDNF^{+/+}$ and $BDNF^{+/Met}$ females belonged to stress sensitive pathways, such as methylation, histone modification, circadian regulation, PI3K-Akt-mTOR, and TNF-NF-kB pathways. Moreover, the analysis of single candidate genes within these pathways highlighted considerable sex differences. These results suggest that the heterozygous variant BDNF Val66Met polymorphism mimics some effects of acute stress in a sex dependent manner and that the CA3 is likely to be a crucial hippocampal region for the establishment of sex differences in animal models of stress-related disorders.

Disclosures: J. Marrocco: None. **M.B. Ríos:** None. **J.F. Kogan:** None. **J.D. Gray:** None. **E.M. Waters:** None. **E.F. Schmidt:** None. **N. Heintz:** None. **B.S. McEwen:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.10/U15

Topic: E.05. Stress and the Brain

Support: IOS-1122074

Title: Sex-dependent programming of opioid receptor expression within the juvenile nucleus accumbens by early life stress

Authors: *L. CHANG[1], S. L. KIGAR[2], A. CUARENTA[2], H. C. GUNDERSON[2], B. A. BALDO[2], V. P. BAKSHI[2], A. P. AUGER[2];
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Abstract: Early life stress (ELS) has been found to modify typical brain development and potentially leading to increased risk for neuropsychiatric disorders, such as depression and

anxiety. Importantly, sex differences are often observed in the prevalence, age of onset, and manifestation of some of these conditions. This suggests that variations in the underlying circuitry between males and females may set up mental health risk or resilience to early life perturbation. Furthermore, many of these disorders present with atypical social reward, often in the form of social anhedonia. As endogenous opioids play an important role in reward-related behaviors, we wanted to investigate if ELS alters typical development of the opioid reward system within the nucleus accumbens, a major site of reward. We modeled ELS by exposing male and female Sprague-Dawley pups to predator odor on postnatal days 1 through 3 for 5 minutes each day. We observed a significant decrease in mu- and kappa-opioid receptor mRNA levels in stressed females compared to control females 30 minutes after the last predator odor exposure. This confirms our hypothesis that ELS does indeed disrupt typical development of the opioid system within the nucleus accumbens. However, there seems to be some specificity in the impact of ELS as it did not alter delta-opioid receptor mRNA levels within this region. Interestingly, ELS had no significant effect on opioid receptor mRNA expression in the male nucleus accumbens, indicating that the impact of ELS on brain development is dictated by biological sex. This suggest that ELS disrupts opioid reward system during neonatal developmental, possibly re-shaping the connections within this system at a crucial time point in a sex-dependent manner. The sex-specific impact of ELS within the developing nucleus accumbens may set up risk or resilience differently for males and females to certain mental disorders with abnormal sociability, such as schizophrenia and depression, or perhaps later addiction. We are currently in the process of determining whether the influence of ELS on the alterations in gene expression is acting through epigenetic mechanisms, and whether these modifications are stable until the juvenile period or transient in the neonatal period.

Disclosures: **L. Chang:** None. **S.L. Kigar:** None. **A. Cuarenta:** None. **H.C. Gunderson:** None. **B.A. Baldo:** None. **V.P. Bakshi:** None. **A.P. Auger:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.11/U16

Topic: E.05. Stress and the Brain

Support: K12HD051953

McMicken STEM Fellow Program for the Department of Psychology

Title: Adolescent psychosocial stress induces immediate and sustained increases in anxiety-like behavior and deficits in social behavior in male rats

Authors: *V. GHISAYS[1], J. STREICHER[2], J. CALDWELL[2], S. BERMAN[2], A. BIRKENHAUER[2], C. ESTRADA[1], M. B. SOLOMON[2];
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Abstract: Social defeat stress is a common problem among adolescents. Several data suggest that social stress increases the susceptibility for psychopathology including anxiety and depression later in adulthood. Here, we examined the immediate and sustained effects of social defeat on anxiety-like, depression-like and social behavior in adolescent male rats. In Experiment 1 male rats were exposed to a battery of behavioral tests including open field, social preference/avoidance test in either neutral, familiar (home cage) or threatening (resident aggressor) environments and social interaction test in their home cage. Testing animals in multiple contexts allows us to extract a more thorough behavioral phenotype in defeated males. This is particularly important, given that many laboratories assess the behavioral consequences of social stress in primarily anxiety-provoking conditions (i.e., open field, forced swim test). Adolescent males exposed to chronic social defeat stress exhibited immediate and sustained (lasting through adulthood) increases in anxiety-like behavior and deficits in social behavior, depending upon the testing environment. For example, deficits in social behavior were more prominent in uncontrollable and threatening environments versus controllable and neutral environments. Notably, defeated adolescents and adult males were more likely to display active coping strategies (defensive burying/digging behaviors towards constrained conspecifics) only in controllable, familiar environments (home cage), but not in a neutral or threatening (aggressor home cage) environments. In Experiment 2 we examined the impact of social defeat on behaviors commonly associated with a depression-like phenotype using the forced swim and olfaction hidden cookie tests. Social defeat did not alter 'helplessness' behavior in the FST nor did it impact the latency to find (appetitive) or consume a cookie. These data confirm the findings of many laboratories indicating that social defeat is a potent stressor in males, but underscore the importance of considering the context in which animals are tested. Given the sustained increases in anxiety-like behaviors in previously defeated adolescent males, these findings may further our understanding of how social stress during the formative years increases susceptibility to psychological disorders in adulthood.

Disclosures: **V. Ghisays:** None. **J. Streicher:** None. **J. Caldwell:** A. Employment/Salary (full or part-time):; University of Cincinnati. **S. Berman:** None. **A. Birkenhauer:** None. **C. Estrada:** None. **M.B. Solomon:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.12/U17

Topic: E.05. Stress and the Brain

Support: start up funds from departments of Psychology and Psychiatry and Behavioral Neuroscience

Title: The role of estradiol signaling in the medial amygdala on emotionality, cognition and metabolic function in female rats

Authors: *C. ESTRADA[1,1], V. GHISAYS[1], J. CALDWELL[2], J. STREICHER[2], S. BERMAN[2], A. BIRKENHAUER[2], M. B. SOLOMON[2];
[1]Psychology, [2]Psychiatry and Behavioral Neurosci., Univ. of Cincinnati, Cincinnati, OH

Abstract: Anxiety and depression are the two most common mental illnesses in the United States. Notably, women are twice as likely as men to suffer from these psychopathologies. Estradiol (E2) exerts potent effects on emotionality in women and female rodents across the reproductive lifespan. Previous data from our laboratory and others indicate that systemic administration of physiologically relevant doses of E2 decreases endocrine stress responses, depression-like and anxiety-like behaviors. The medial amygdala (MeA) mediates fear and endocrine stress responses, arousal, and affiliative behaviors in male and female rodents. Of note, reduced estrogen receptor (ER) α expression in the MeA is temporally associated with anxiogenic and depressive-like behavior in postpartum rats, suggesting that decreased ER signaling in the MeA contributes to anxiety-like and depression-like behaviors in females. The goal of the present study was to do an in-depth behavioral assessment of the impact of estradiol signaling specifically in the MeA on emotionality and cognition in both nonsocial and social behavioral assays. We accomplished this goal using adult ovariectomized females with bilateral E2 or cholesterol micropellets aimed at the MeA. Following adequate recovery from surgery, females were exposed to a battery of behavioral tasks designed to gauge different aspects of anxiety-like, cognitive and depression-like behaviors including the open field, novel object recognition, social preference/recognition, social interaction and forced swim tests. Contrary to our hypothesis, E2 signaling in the MeA had marginal effects on behavioral indices of emotionality and cognitive function. However, E2 signaling in the MeA significantly decreased body weight gain, food intake and visceral adiposity in ovariectomized females relative to those receiving bilateral MeA implants of cholesterol. Notably, previous work highlights a critical role for the MeA in body weight regulation in rodents. Given the prominent role of systemic E2 for being metabolically beneficial in rodent models of obesity, these data highlight the MeA as a critical node for the E2 mediated effects on metabolic function. In an effort to understand how E2 signaling in the MeA regulates energy homeostasis in ovariectomized females, we are

currently examining neuronal activity in hypothalamic and brainstem regions known to regulate feeding and/or body weight regulation.

Disclosures: **C. Estrada:** None. **V. Ghisays:** None. **J. Caldwell:** A. Employment/Salary (full or part-time):; University of Cincinnati. **J. Streicher:** None. **S. Berman:** None. **A. Birkenhauer:** None. **M.B. Solomon:** A. Employment/Salary (full or part-time):; University of Cincinnati.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.13/U18

Topic: E.05. Stress and the Brain

Support: Corcept Therapeutics Incorporated

5T32NS007453-15

Title: Neuroendocrine and behavioral effects of CORT 118335, a novel glucocorticoid and mineralocorticoid receptor antagonist in male rats

Authors: ***E. T. NGUYEN**, S. BERMAN, J. STREICHER, A. C. WULSIN, J. CALDWELL, J. P. HERMAN, M. B. SOLOMON;
Dept. of Psychiatry and Behavioral Neurosci., Univ. of Cincinnati, Cincinnati, OH

Abstract: Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis due to aberrant glucocorticoid secretion is associated with psychopathology. Consistent with this fact, compounds targeting both Type I (mineralocorticoid MR) and Type II (glucocorticoid GR) corticosteroid receptors are being advanced as putative antidepressants or anxiolytics. Previous findings from our laboratory indicate that compounds selectively targeting GR decrease both neuroendocrine and behavioral (depression-like) responses to stress in male rats. The goal of the present study was to determine the impact of GR/MR antagonism on neuroendocrine and behavioral responses to stress in male rats. This was accomplished by using CORT 118335, a dual GR/MR antagonist. In two separate experiments, adult male rats were treated for 5 days with vehicle, CORT 118335 (10mg/kg or 30mg/kg), or imipramine (10mg/kg) (tricyclic antidepressant) and exposed to either restraint stress or the forced swim test (FST). Relative to vehicle, both doses of CORT 118335 potently suppressed neuroendocrine responses to restraint and FST stress exposure. The decreased neuroendocrine output in animals treated with CORT

118335 was not accompanied by an antidepressant-like effect of the compound in the FST, as there was no difference in immobility between animals treated with this compound versus vehicle. Consistent with our previous findings, imipramine (positive control) modestly decreased neuroendocrine responses to both restraint stress and FST relative to animals treated with vehicle and decreased immobility in the FST, consistent with antidepressant effects. Notably, inactivation of the infralimbic cortex (IL) decreases depression-like behavior in rats and in alignment with the behavioral observations, imipramine decreased c-Fos immunolabeling in the IL. Taken together, the data suggest dissociation between corticosterone responses and immobility in the FST. The data further suggest that compounds targeting both MR/GR may be useful for mitigating glucocorticoid hyper-secretion to stress, but their ability to modulate mood-like responses to stress (at least under the context of the present study) may be limited.

Disclosures: **E.T. Nguyen:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Corcept Therapeutics Incorporated. **S. Berman:** None. **J. Streicher:** None. **A.C. Wulsin:** None. **J. Caldwell:** None. **J.P. Herman:** None. **M.B. Solomon:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Corcept Therapeutics Incorporated. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Corcept Therapeutics Incorporated.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.14/U19

Topic: F.02. Animal Cognition and Behavior

Support: ONR Grant N00014-09-1-0598

ONR Grant N00014-12-1-0366

National Institute of Mental Health Grant R01MH104261

Pritzker Neuropsychiatric Disorders Research Constortium

Hope for Depression Research Foundation

Rackham Predoctoral Fellowship

Title: Learning in the company of individuals with similar phenotypes can facilitate fear extinction in rats selectively bred for their locomotor response to novelty

Authors: *K. E. PRATER[1,2], E. L. AURBACH[1,2], H. LARCINESE[2], P. BLANDINO, Jr.[2], S. J. WATSON[2], S. MAREN[3], H. AKIL[2];
[1]Neurosci. Grad. Program, [2]Mol. and Behavioral Neurosci. Inst., Univ. of Michigan, Ann Arbor, MI; [3]Psychology, Texas A&M Univ., College Station, TX

Abstract: As we search for new treatments for anxiety disorders, it is important to understand why certain individuals are more vulnerable to developing PTSD after a traumatic event and how we can help vulnerable individuals improve their prognosis. We believe that our rat model of individual differences in locomotor response to a novel environment provides insight into vulnerability and resilience to anxiety disorders. In experiment one, rats selectively bred for high (bHR) or low (bLR) locomotor response to a novel environment and rats from the F1 generation of a bHR-bLR cross (bIRs), which display an intermediate locomotor phenotype, received a standard fear conditioning and extinction paradigm. bLRs demonstrated decreased extinction learning and extinction retention compared to bIRs and bHRs, while bHRs exhibited faster extinction and greater retention than bIRs. This indicates that bLRs, like PTSD patients, may be vulnerable to maladaptive fear behaviors, while bHRs may be more resilient. In a second study, it was found that although bLR extinction learning remains deficient compared to bHRs, grouping animals solely with their in-group phenotype during fear conditioning and extinction results in increased extinction learning compared with animals trained in isolated pairs or mixed phenotypes. We are replicating these findings, and studying the neural correlates underlying these differences in extinction learning. These results may have significant implications for the study of fear behavior in animals and humans, as individual differences in temperament may significantly impact fear extinction learning.

Disclosures: K.E. Prater: None. **E.L. Aurbach:** None. **H. Larcinese:** None. **P. Blandino:** None. **S.J. Watson:** None. **S. Maren:** None. **H. Akil:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.15/U20

Topic: F.02. Animal Cognition and Behavior

Support: CIHR MOP-246144

Title: GPR55 receptor activation in the ventral hippocampus modulates mesolimbic dopaminergic activity and causes schizophrenia-related emotional and social cognition disturbances

Authors: *S. R. LAVIOLETTE[1], M. LOUREIRO[2], J. RENARD[2];
[2]Anat. & Cell Biol., [1]Univ. of Western Ontario, London, ON, Canada

Abstract: Disturbances in the brains endocannabinoid signaling system are linked to schizophrenia-related symptomology. Cannabinoids produce their central actions primarily via the CB1 receptor (CB1R). However, emerging evidence points to the existence of novel cannabinoid-sensitive targets, such as the G protein-coupled receptor-55 (GPR55R). Interestingly, it has been proposed that deleterious emotional/cognitive side effects associated with cannabinoid-based pharmacotherapies such as rimonabant, may be related to effects on the GPR55 receptor. Nevertheless, the potential role of GPR55 in modulating mesolimbic dopamine (DA) activity and associated emotional processing and social cognition behaviours is unknown. GPR55R is expressed in the hippocampus, in humans and rodents. Pre-synpatic GPR55R's are also known to regulate glutamate (GLUT) release within the mammalian hippocampus (Sylantyev et al., 2013). The ventral hippocampus (vHIPP) plays an integral role in the formation of emotional associative memories through interactions with the mesolimbic dopamine (DA) system. We have previously shown that intra-vHIPP stimulation of cannabinoid CB1 receptor transmission strongly modulates the activity of dopaminergic (DA) neurons in the ventral tegmental area (VTA) and nucleus accumbens (NAc). In the present study, we tested whether activation of the GPR55R directly within the vHIPP was able to 1) modulate VTA DAergic neuronal activity and/or 2) influence the formation of emotional associative memories and social behaviours/cognition. Using *in vivo* electrophysiological recordings in rats, we found that intra-vHIPP microinfusions of palmitoylethanolamide (PEA), an endogenous lipid that acts as a selective GPR55 agonist, potently increased VTA DA neuron firing and bursting activity. Furthermore, GPR55 activation profoundly disrupted natural sociability and social recognition memory. In addition, intra-vHIPP GPR55 activation altered the formation of context-dependent fear memory. While co-infusion of the selective GPR55 antagonist (CID16020046) blocked the behavioral effects induced by intra-vHipp PEA, co-infusion of a selective CB1R antagonist failed to modulate GPR55-mediated effects. Furthermore, co-infusion with a selective NMDA receptor antagonist, completely blocked the behavioural deficits induced by intra-vHIPP GPR55 activation, demonstrating a functional role for GLUTergic transmission in the effects of GPR55 within the vHIPP. Our data add critical new insights into the role of the GPR55 receptor in DA-related behaviors and emotional regulation known to be disturbed in neuropsychiatric disorders.

Disclosures: S.R. Laviolette: None. **M. Loureiro:** None. **J. Renard:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.16/U21

Topic: E.05. Stress and the Brain

Support: MH092438

Title: Corticotropin-releasing factor activates different circuits in male and female rats

Authors: *K. WIERSIELIS, S. COHEN, G. VAN BUSKIRK, D. LOSEN, H. KEITA, J. BERGMANN, N. BAKSH, B. WICKS, D. BANGASSER;
Temple Univ., Philadelphia, PA

Abstract: Stress-related psychiatric disorders, such as anxiety and depression, occur twice as frequently in women than in men. Corticotropin-releasing factor (CRF) orchestrates the stress response and is dysregulated in these disorders. Thus, sex differences in responses to CRF could contribute to the sex bias in disease prevalence. We previously identified sex differences in CRF1 receptor signaling and trafficking in the locus coeruleus (LC) that rendered the electrophysiological responses of female LC neurons more sensitive to CRF than those of male rodents. However, the extent of sex differences in CRF sensitivity has not been systematically explored. Here we begin to address this question by examining how the central administration of ovine CRF differentially activates stress-related brain regions in adult male and female rats using the immediate early gene, cFOS. Because many sex differences are mediated by circulating ovarian hormones, central CRF or vehicle was administered to females in the proestrus phase of the estrous cycle (higher estrogen and progesterone levels), females in the diestrus phase (lower estrogen and progesterone levels), and gonadally intact males. Our results revealed that although for some brain regions, such as the paraventricular nucleus of the hypothalamus, CRF increased cFOS expression relative to vehicle treatment in all groups, most brain regions showed sex and cycle stage-specific effects of CRF on neuronal activation. For example, CRF increased cFOS in diestrus females, but not proestrus females or males, in several brain regions, including the periaquductal gray, ventromedial dorsal raphe, and the laterodorsal tegmental nuclei. Conversely, the basal nucleus and the nucleus accumbens of proestrus females and males had more cFOS profiles than did diestrus females following central CRF administration. In the LC there was no effect of cycle, but rather females had more CRF-induced cFOS profiles than males, a result consistent with our predictions based on previous studies. Collectively, these findings indicate that central CRF administration activates different circuits in males and females, and that differences are further revealed across the female estrous cycle. Surprisingly, although cFOS has been widely used, previous studies were almost exclusively conducted with male rats. Thus, sex differences in the activation of brain circuits by stressors, neuropeptides, and other stimuli, may be an important, but underexplored, determinant of sex differences in behavior and pathology.

Disclosures: **K. Wiersielis:** None. **S. Cohen:** None. **G. Van Buskirk:** None. **D. Losen:** None. **H. Keita:** None. **J. Bergmann:** None. **N. Baksh:** None. **B. Wicks:** None. **D. Bangasser:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.17/U22

Topic: E.05. Stress and the Brain

Support: TIFR, Department of Atomic Energy

Title: Sexual dimorphism in the pattern of c-Fos activation evoked by acute and chronic stress

Authors: ***A. SOOD**, K. CHAUDHARI, N. KACHEWAR, V. VAIDYA;
Tata Inst. of Fundamental Res., Mumbai, India

Abstract: Stressful events have profound effects on the physiology and behavior of an organism. The nature (physical or psychological), severity (severe or mild) and duration (acute or chronic) of the stressor determine to a large extent, if the response elicited will be adaptive or maladaptive. The brain apart from perceiving and orchestrating the stress response is also a target of stress. While acute stress enhances immune function and facilitates formation of memories pertaining to emotional events, chronic stressors lead to memory impairment and atrophy of the apical dendrites of the pyramidal neurons of the CA3 region of the hippocampus. Though sexual dimorphism in the physiological and behavioral responses to stress has been characterized in rodents and monkeys, sex based differences in the pattern of neuronal circuit activation evoked by stress remain poorly understood. In the present study we have used c-Fos as a marker of neuronal activity to examine the activation pattern of different brain regions in male and female rats exposed to either an acute or chronic stress regime. We used immobilization for 2 hours [Acute Immobilization Stress (AIS)] or forced swim (FS) as acute stressors or immobilization for 2 hours each day for 10 consecutive days [Chronic Immobilization Stress (CIS)] as a chronic stressor. While the pattern of CIS evoked changes in c-Fos expression was similar among males and females in brain regions like the Paraventricular nucleus of the hypothalamus (PVN) and Habenula, we noted sexual dimorphism in the medial prefrontal cortex (mPFC) and specific hippocampal subfields. We observed that CIS led to a significant decrease in the number of c-Fos positive cells in the medial prefrontal cortex (mPFC) of females but not in males. CIS also caused a decline in the number of c-Fos positive cells in the DG of both males and females but in the CA3 region of only females. In addition, we observed that the baseline

activity is lower in the dentate gyrus (DG), but higher in the CA3 region of females compared to males. Since different neuronal circuits involved in the stress response are organized into functional networks, we are in the process of performing cross correlation analysis to look at functional connectivity between different brain regions that may vary in a sexually dimorphic manner. We are also using retrograde neuronal tracing techniques to understand the contribution of different afferent inputs in the activation of the mPFC- a brain region known to be activated by acute stress.

Disclosures: **A. Sood:** None. **K. Chaudhari:** None. **N. Kachewar:** None. **V. Vaidya:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.18/U23

Topic: E.05. Stress and the Brain

Support: Institute for Molecular Neuroscience

Howard Hughes Medical Institute

Title: TIA-1 is a prion-related RNA binding protein that regulates alternative splicing of the glucocorticoid receptor in a sex-specific manner

Authors: ***J. B. RAYMAN**, E. R. KANDEL;
Neurosci., Columbia University/HHMI, New York, NY

Abstract: Post-traumatic stress disorder (PTSD) arises from an interplay of genetic and environmental factors. To explore the molecular neurobiology of gene × environment interaction in the context of PTSD, we developed a mouse model for stress vulnerability based on deletion of TIA-1, a prion-related RNA binding protein that is involved in cellular stress. Among its many roles in RNA metabolism, TIA-1 facilitates the preferential translation of mRNAs required to contend with environmental challenge. Previous observations that cellular stress can be induced by prolonged exposure to high levels of glucocorticoids led us to hypothesize that TIA-1 operates at the nexus of systemic and cellular stress. By dismantling the cellular stress response through deletion of TIA-1, we reasoned that a key homeostatic feedback mechanism would be lost, leading to the development of maladaptive behavioral changes. Here, we find that naive TIA-1 KO mice are indistinguishable from wild-type controls in all behavioral measures evaluated thus far. However, several weeks after exposure to contextual fear conditioning, TIA-1

KO mice demonstrate increased anxiety and avoidance behavior compared to wild-type littermates. Electrophysiological studies reveal aberrant synaptic plasticity in the ventral hippocampus of TIA-1 KO animals in response to corticosterone treatment, consistent with a role for TIA-1 in normal emotional memory formation during stress. In addition, molecular data suggest that TIA-1 regulates alternative splicing of the glucocorticoid receptor, which is known to be important for hippocampal synaptic plasticity during stress. Interestingly, the latter effects are all female-specific. Finally, preliminary data indicate that prion-like aggregation of TIA-1 is critical for dynamic splicing of the glucocorticoid receptor during stress. In summary, TIA-1 actively modulates glucocorticoid-dependent signaling in the female brain in response to glucocorticoid exposure. Our results may provide new insights into a second functional prion in brain that has a role in the biology of stress-related psychiatric illness.

Disclosures: J.B. Rayman: None. **E.R. Kandel:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

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Program#/Poster#: 615.19/U24

Topic: E.05. Stress and the Brain

Support: NSF grant IOS 1146853

LA Board of Regents - LEQSF(2012-17)-GF-15

Title: Sex-specific molecular plasticity in the rodent hippocampus following chronic variable stress

Authors: *D. R. HOMIACK[1], M. STANLEY[1], B. BARRILEAUX[2], N. LIM[1], L. SCHRADER[1,2];
[1]Neurosci., [2]Cell and Mol. Biol., Tulane Univ., New Orleans, LA

Abstract: In animal models, chronic stress or glucocorticoid treatment can induce depressive-like behavior in male rodents. In addition to anhedonic behaviors, chronic stress causes impairments in spatial memory and structural plasticity in the male hippocampal formation. In spite of the gender disparities observed in major depressive disorder in the human population, previous rodent studies largely find that female rodents are less affected by chronic stress than male rodents. The molecular alterations caused by chronic stress in the hippocampal formation are poorly characterized, particularly in female rodents. Here we report that chronic variable

stress (CVS) causes sex-specific alterations in the extracellular-signal-regulated kinase (ERK/MAPK) and adenosine-monophosphate-activated protein kinase (AMPK) pathways following chronic variable stress (CVS) in the hippocampus of intact rats. CVS exposure reduced phosphorylation of ERK/MAPK and its downstream target, cyclic-AMP-response element binding protein (CREB), throughout the male, but not female hippocampus. Reductions in phosphorylated CREB were not due to decreased protein kinase A (PKA) activity, as phosphorylated PKA substrate was either unchanged or increased throughout the male and female hippocampus of CVS-exposed animals. Sirtuin1 is a protein deacetylase involved in energy metabolism, which has increased activity, but not expression following CVS in the male DG (Ferland et al., 2013). Consistent with our previous findings, acetylation of the SIRT1 substrate, p53, was reduced in the male but not female DG. Concordantly, CVS increased AMPK substrate phosphorylation in the male DG. Interestingly, neither acetylated p53 nor AMPK substrate were affected by CVS in the female DG. Our findings implicate DG-localized AMPK as an upstream activator of SIRT1 and a potential molecular regulator of depressive-like behavior in male animals. Additionally, these results provide molecular evidence of stress resilience in the female hippocampus.

Disclosures: D.R. Homiack: None. **M. Stanley:** None. **B. Barrileaux:** None. **N. Lim:** None. **L. Schrader:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

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Topic: E.05. Stress and the Brain

Support: NIH Grant DA008259

NIH Grant HL098351

NIH Grant HL06571

NIH Grant DA007274

Title: Baseline and chronic stress induced sex differences in rat CA3 hippocampal pyramidal cell dendrite morphology and delta opioid receptor trafficking

Authors: *S. ODELL[1], B. HALL[1], S. MAZID[1], T. A. VAN KEMPEN[1], A. D. GONZALEZ[1], B. S. MCEWEN[2], E. M. WATERS[2], T. MILNER[1,2];

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Abstract: Opioid system dynamics in the rat hippocampus are highly sex dependent, as the hormonal milieu modulates opioid peptide levels, mu-opioid and delta-opioid receptor (DOR) trafficking in select populations of neurons and opioid-dependent long-term potentiation. Further, our recent studies have shown that sex differentially affects the response of the hippocampal opioid system to chronic stress (Pierce et al., 2014; Milner et al., 2013). Previous studies have established that DOR trafficking and density have baseline sex differences in hippocampal CA1 pyramidal cell dendrites (Williams et al., 2011). The current study aimed to investigate whether sex and/or chronic stress affected DOR distributions in CA3 region, as this region is important in context learning and therefore the establishment of addiction behaviors. Male and diestrus female rats were subjected to 10 days of chronic immobilization stress (CIS), followed by brain perfusion and fixation with acrolein and paraformaldehyde. Hippocampal sections were labeled for DOR (with silver intensified immunogold particles; SIG) using dual labeling immunohistochemistry and the subcellular distribution of DOR in CA3 pyramidal cell dendrites in stratum radiatum was analyzed using electron microscopy. In control (unstressed) rats, males exhibited significantly larger pyramidal cell dendrites, increased number of plasmalemmal DOR SIGs, but significantly decreased density of cytoplasmic and total DOR SIGs in pyramidal cell dendrites. This latter finding suggests that at baseline levels, males have fewer reserve pools of DORs. Following CIS, males displayed no significant changes in the morphology of CA3 pyramidal cell dendrites, while females showed increases in pyramidal cell diameter. Males had a decreased proportion of plasmalemmal DOR SIGs while females displayed no change in plasmalemma DOR SIGs on pyramidal cell dendrites. Moreover, CIS in females decreased DOR SIG cytoplasmic and total density to the levels seen in control and CIS males. These findings suggest that after CIS, fewer DORs are available for binding on pyramidal cell dendrites in males and that the reserve pools of DORs in pyramidal cell dendrites in females have been trafficked to other locations. These changes may contribute to sex differences in learning mechanisms leading to the acquisition and/or relapse of drug addiction.

Disclosures: **S. Odell:** None. **B. Hall:** None. **S. Mazid:** None. **T.A. Van Kempen:** None. **A.D. Gonzalez:** None. **B.S. McEwen:** None. **E.M. Waters:** None. **T. Milner:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.21/U26

Topic: E.05. Stress and the Brain

Support: National Institutes for Health; Grant Number: R21MH091445-01

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National Institutes for Health; Grant Number: R25GM097634-01 (BP-ENDURE)

Title: Social isolation during adolescence alters dendritic branching and spine density of pyramidal neurons in the hippocampal CA1 of adolescent female rats

Authors: *R. ADEROGBA[1,2], A. AKAD[2], F. SHAEFFER[2], W. HUANG[2], A. RAO[2], L. KLINGENSMITH[2], Y.-W. CHEN[2], T. CHOWDHURY[2], C. AOKI[2];
[1]CUNY Hunter Col., New York, NY; [2]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Social isolation during the vulnerable period of adolescence produces behavioral, physical, and biochemical alterations. The hippocampus is a component in the limbic system that plays a role in spatial learning, memory, anxiety and regulation of stress. Interestingly, previous studies indicate that stress causes differential response in hippocampal sub-regions. The effects of stress have been shown to be gender specific. For example, females are more susceptible to stress-increased anxiety-related behaviors. Here, we tested the effects of social isolation during adolescence (postnatal days 36-44) upon 8 Sprague-Dawley female rats, compared to 8 age-matched pair-housed female rats. In particular, we conducted 3-D Sholl analysis of pyramidal neurons after the Golgi procedure, to quantify dendritic branching and followed this by spine density analysis, using the Neurolucida system. In the caudal-ventral hippocampus, which preferentially regulates anxiety, social isolation evoked an increase in dendritic branching in stratum radiatum (SR) but lowered spine density, compared to the paired controls. No change was detected in stratum lacunosum-moleculare (SLM). In the rostral-dorsal hippocampus, which preferentially mediates spatial learning and contextual memory, social isolation reduced both dendritic branches and spine density in SR, indicating a net loss in the spine number. Again, no change was detected in the SLM. Comparisons of the anatomical subdivisions of the hippocampus revealed that pyramidal neurons of the rostral-dorsal hippocampus of control rats exhibit greater dendritic branching in SR than pyramidal neurons of the caudal-ventral hippocampus. This regional difference was absent within the SR of singly housed rats, due to decreased branching in the rostral-dorsal subdivision and increased branching of the caudal-ventral region. Conversely, SLM of the dorsal-rostral region of socially isolated rats showed more branching than SLM of the caudal-ventral region. Together, our data indicate that social isolation of adolescent females elicits pathway-specific changes in the hippocampus that affect

both the rostral-dorsal and caudal-ventral hippocampus. This morphological change may contribute towards altered spatial and contextual memory performance as well as anxiety regulation.

Disclosures: **R. Aderogba:** None. **A. Akad:** None. **F. Shaeffer:** None. **W. Huang:** None. **A. Rao:** None. **L. Klingensmith:** None. **Y. Chen:** None. **T. Chowdhury:** None. **C. Aoki:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 615.22/U27

Topic: E.05. Stress and the Brain

Support: DGAPA IA2015-15

CONACYT- 180009

Title: Neonatal maternal separation alters, in a gender specific manner, the expression of regulatory elements of the TRH system and the response of the thyroid axis to energy deficiency

Authors: *E. L. JAIMES, M. GUTIÉRREZ-MARISCAL, P. JOSEPH-BRAVO;
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Abstract: Neonatal maternal separation (MS) induces a functional adaptation of the hypothalamic-pituitary-adrenal axis (HPA), leading to epigenetic changes that alter the stress response in adult life. As the activity of the HP-thyroid (HPT) axis is susceptible to various forms of stress, we studied if MS during the lactation period altered HPT axis function and its response to a situation of negative energy balance such as fasting in the female adult rat. Wistar dams were divided into a naïve (N) or a MS group. From PD 2 -21, pups in the MS group were separated from their mothers 3h/day. At PD60, rats were housed 2/cage, and half of the N and MS rats were fasted for 48 h. Trh mRNA levels were quantified in coronal brain sections of the rostrocaudal extent of the paraventricular nucleus (PVN) by *in situ* hybridization. Adenohypophyseal TRH-R1, pyroglutamyl peptidase II (PPII) and TSH-β mRNA were semi-quantified by RT-PCR and, serum hormones by radioimmunoassays or ELISA. Gender differences were observed in the fasting response of N rats; the decrease in body weight, Trh expression, and T3 or the increase in corticosterone serum concentrations, were higher in females than in males. MS increased white adipose tissue mass and leptin levels only in females. Altered basal expression of key elements involved in HPT function was produced by MS:

increased Trh mRNA expression compared to the N group in the medial (m)PVN; diminished TRH-R1 and TSH-β mRNA in the adenohypophysis, and in serum T3 levels albeit the latter, only slightly. In response to fasting, MS rats lost significantly less body weight than the N group, without reducing body fat. Fasting induced changes were of smaller magnitude in MS rats compared to N, whether female or males; these include the decrease in mid-PVN Trh expression, increased that of TRHR1 in adenohypophysis; and expected reduction in D1 liver activity was blunted. These changes were also stronger in MS female than in male rats; the former showed increased white adipose tissue mass and leptin levels. In conclusion, maternal separation can alter the expression of genes that control TRH levels in the neuroendocrine axis, and may interfere with peripheral aspects of thyroid hormones turnover. The activity of the HPT axis is altered at adult stage in response to a 48 h fasting in the MS group which may contribute to a metabolic adaptation that leads to low body weight loss.

Disclosures: **E.L. Jaimes:** None. **M. Gutiérrez-Mariscal:** None. **P. Joseph-Bravo:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

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Program#/Poster#: 615.23/U28

Topic: E.05. Stress and the Brain

Support: Supported by DGAPA UNAM, PAPIIT: IN300806

Title: Behavioral and hormonal role of the individual components of the task elevated T maze (ETM) in female rats

Authors: ***N. L. GARCIA SALDIVAR**, M. R. A. GONZÁLEZ LÓPEZ, S. E. CRUZ MORALES;
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Abstract: Exposure to different tasks to evaluate behavior (learning, memory, anxiety) may induce stress, probably related to the presence of aversive components of the procedure. The elevated T-maze (ETM) allows to measure anxiety, learning and memory through a combination of escape (E) and avoidance (AV) trials in two brief sessions. The ETM consist of one enclosed and two open arms, the open arms are the main aversive component. In male rats the exposure to avoidance trials increases corticosterone concentration in plasma, but no in escape. In female rats, the response to stress of the HPA axis is dependent of the estrous cycle. The objective of this study was to evaluate the anxiety and corticosterone levels in female rats during diestrous

(D2) and proestrus (P), by the exposure of different arrays in the ETM. Wistar female rats in D2 and P were exposed to the ETM in different conditions: groups exposed to conventional training (T) consisting of three avoidance and one escape trials (D2-T, P-T); groups exposed only to the avoidance trials (D2-AV, P-AV); groups exposed only to the escape (D2-E, P-E); additionally, intact groups were used as control (D2C, PC). After behavioral procedures, the subjects were sacrificed and blood samples were obtained to measure corticosterone (ELISA). As expected no significant differences in avoidance latencies were detected in the groups exposed to training (D2-T, P-T) and those exposed only to avoidance trials (D2-AV, P-AV). For escape latencies significant differences were detected, the P group showed higher latencies compared with all other groups. Corticosterone levels increased significantly in D2-AV and P-AV groups compared with their respective controls (D2-C, P-C) and trained groups D2-T and P-T. For escape the concentration of corticosterone were higher for D2-E compared with D2-C. The changes observed in escape latencies and costicosterone levels were dependent of the presence or not of avoidance trials. The P-E showed less anxiety than the D2-E; this could be explained by the difference in levels of gonadal hormones in these two phases. It is concluded that exposure to the ETM induce anxiety that is dependent upon the estrous cycle and arrangement of escape trials regarding avoidances.

Disclosures: **N.L. Garcia Saldivar:** None. **M.R.A. González López:** None. **S.E. Cruz Morales:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

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Topic: E.05. Stress and the Brain

Support: MH-090420

MH-093981

Title: Locus coeruleus (LC) neuronal activity and sniffing behavior in female rats during social interaction (SI): impact of adolescent social isolation

Authors: *A. L. CURTIS;
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Abstract: Social interactions are core aspects of human interpersonal skills. Dysfunctional social interactions are typically associated with a range of anxiety disorders which, in turn, are salient elements of certain psychiatric and personality disorders. A critical window for disruption of brain development through which events can have an enduring impact that affect behaviors and cognition in adulthood is adolescence. Social isolation during adolescence has sex specific effects such that for female rats, it increases stress responsiveness and predisposes to anxiety-like behaviors in adulthood. The present study investigated the long term effects of adolescent social isolation of female rats on social interactions in adulthood. Because our previous studies suggested that social stress during adolescence had long term effects on activity of LC-NE neurons, LC activity before and during social interactions were compared between females exposed to adolescent social isolation and group housed controls. Female adolescent rats were housed in isolation (PND30-50) and then group housed. Controls remained group housed throughout adolescence and adulthood. Starting at 70 days of age, all rats were implanted with a microwire bundle to record LC neuronal activity. Rats were placed in an open field alone and LC activity and behavior were recorded for 10 min (baseline values). At this time a weight-matched stimulus female rat was placed in the field and social interactions were quantified while recording LC activity for another 10 min (interaction values). In stressed rats, LC discharge rate robustly increased over the LC rate in controls by a factor of two, while basal LC spontaneous rates were similar. In general, interactive behavior of both groups of test rats were not different in type nor total time with sniffing representing 80% of total interactive behavior. However, total time of face sniffing was greater and the duration of the individual face sniffing events were longer for stressed vs. control rats. Linkage between LC activity and sniffing behavior was suggested by further peaks of LC activity superimposed on the already robust LC activity occurring immediatedly before and after, not during, a sniffing event in the stressed females, but not in controls. In conclusion, the robust elevation in LC activity coincident with increased sniffing behavior for stressed females suggests that isolation stress may increase interactive urgency and the saliency of social stimuli. For isolation-stressed females, appropriate interactive behavior and social rank recognition may be disrupted by an urgency for face sniffing.

Disclosures: A.L. Curtis: None.

Poster

615. Sex and Social Factors in Fear and Anxiety

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Topic: F.02. Animal Cognition and Behavior

Support: PUCPR Grant to DLRO

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Title: Estrogen as a neuroprotector against negative effects of morphine in fear extinction

Authors: *F. RODRIGUEZ-ORTIZ[1], A. TORRES-REVERÓN[2], E. SANTINI[3], D. L. RAMOS-ORTOLAZA[1];
[1]Biol., Pontifical Catholic Univ. of Puerto Rico, Ponce, PR; [2]Ponce Hlth. Sci. Univ., Ponce, PR; [3]Palm Beach Atlantic Univ., West Palm Beach, FL

Abstract: Morphine is an opiate primarily used to treat pain. High and frequent doses of morphine can lead to dependence and, eventually might lead to mood and anxiety disorders as well. Previous animal studies using a model of post traumatic stress disorder have suggested that morphine dependence could negatively affect recovery from this disorder in males but not females. Specifically, it was shown that morphine dependent male rats, but not females, continue to show fear upon presentation of a tone associated with a foot shock. Based on the notion that estrogen may be a neuroprotector, this study was aimed at determining whether lower levels of estrogen receptors on male brains, particularly in the nucleus accumbens (NAc), would be related to the persistent fear observed in these morphine-dependent animals. To achieve this, brains from morphine-dependent and saline control male and female Sprague Dawley rats were dissected after cued fear conditioning and extinction. Proteins were extracted and separated by SDS-PAGE and transferred to nitrocellulose membranes. Western Blots were performed to measure levels of estrogen receptors (ER) subtypes α and β. Our results showed high levels of ERα in the NAc of morphine-dependent female rats compared to morphine-dependent males and controls. Preliminary results do not show changes in ERβ levels. Given the neuroprotective role of estrogen, our results suggest that higher levels of ERα in the NAc of morphine-dependent females protect them so that they are able to recover from a previous traumatic experience. Males' persistent fear, on the other hand, could be due to the significantly lower levels of these receptors in the brain. These results suggest an important role of sex hormones in behavioral responses to morphine dependence, particularly with regards to the persistence of fear and anxiety disorders. It seems like activation of estrogen receptors might help reduce the fear and manage some of the adverse effects of chronic morphine in the brain.

Disclosures: F. Rodriguez-Ortiz: None. **A. Torres-Reverón:** None. **E. Santini:** None. **D.L. Ramos-Ortolaza:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: E.05. Stress and the Brain

Support: HL 112350

NIU Graduate School

Title: Combined vicarious stress and social buffering in the prairie vole

Authors: *J. J. WARDWELL[1], N. MCNEAL[2], M.-A. L. SCOTTI[2], W. COLBURN[2], A. DOTSON[2], E. IHM[2], M. WOODBURY[2], A. J. GRIPPO[2];
[1]Psychology PM 328, Northern Illinois Univ., Dekalb, IL; [2]Northern Illinois Univ., DeKalb, IL

Abstract: Stress is highly pervasive within modern society, and has been associated with many adverse psychological and physiological health effects. In social species, research has shown that the stress level of one individual can affect another, with lower-stress animals attenuating the stress of higher-stress animals (social buffering), and higher-stress animals amplifying the stress of lower-stress animals (vicarious stress). The underlying mechanisms of these phenomena however, are less understood. The current study examined the behavioral and physiological effects of two animals simultaneously experiencing a stressor from two different perspectives (one directly and one indirectly) in a highly gregarious rodent species, the prairie vole (Microtus ochrogaster). This species is unique amongst rodents because it shares many behavioral and physiological properties with humans, including monogamy, bi-parental care of offspring, as well as autonomic cardiac and hormonal regulation. It was hypothesized that animals directly experiencing a species-relevant stressor with a comparatively less-stressed sibling observing would exhibit an attenuated stress response when compared to animals directly experiencing the stressor alone. It was also hypothesized that observer animals that were indirectly exposed to a sibling experiencing a stressor would exhibit an elevated stress response when compared to animals that did not. To test this, adult male sibling prairie voles were placed in a testing apparatus where one animal directly experienced a stressor (the tail suspension test), while the other could freely observe within the confines of an open field. Control animals experienced the tail suspension test or open field, but did so in isolation. Physiological and behavioral results indicate that the direct experience of a stressor without the benefit of a comparatively less-stressed sibling present was the most distressing condition, while exposure to the open field without observing a sibling experience a tail suspension test was the least distressing. Physiological stress response measures were found to be significantly ($p<0.05$) elevated in animals that observed a sibling experience a stressor when compared to those that did not. The current study suggests that social buffering and vicarious stress effects can occur at the same

time, in response to the same stressor. With further research utilizing this animal model, it is possible that a greater understanding of the mechanisms behind these stress effects can be reached.

Disclosures: J.J. Wardwell: None. **N. McNeal:** None. **M.L. Scotti:** None. **W. Colburn:** None. **A. Dotson:** None. **E. Ihm:** None. **M. Woodbury:** None. **A.J. Grippo:** None.

Poster

615. Sex and Social Factors in Fear and Anxiety

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Topic: E.05. Stress and the Brain

Support: NSERC Grant 311637

Title: Effects of extended developmental and adult social isolation on neurochemistry and cortisol levels in response to a social stimulus in zebrafish (Danio rerio)

Authors: *S. SHAMS[1], D. CHATTERJEE[2], R. GERLAI[2,3];
[1]Cell & Systems Biol., [2]Psychology Dept., Univ. of Toronto Mississauga, Mississauga, ON, Canada; [3]Cell & Systems Biol., Univ. of Toronto Mississauga, Mississuaga, ON, Canada

Abstract: Social isolation models exist in rodents, birds, and non-human primates, where social deprivation leads to deficits in development and/or maintenance of behavioural, physiological, and neural indices. The zebrafish is a highly social species. A wide range of sophisticated genetic techniques are available for the zebrafish, and thus this species may be an excellent translational tool for the exploration of the mechanisms of social behaviour of vertebrates. Similar to other model animals, changes in the social environment of zebrafish can significantly affect subsequent development and expression of behaviour and brain function. To investigate how social isolation affects zebrafish, we studied the effects of extended social isolation (6 months) in both adult and developing zebrafish and compared them with group-housed control. Developmental social isolation started immediately after fertilization, where embryos were separated and kept deprived of all visual and tactile contact with conspecifics. Adult isolation groups were raised in social groups until reaching sexual maturity and then isolated for 6 months, while social control fish remained in groups of five fish throughout their development and adulthood. We exposed these groups of isolated and control fish to a social stimulus, animated moving images of five zebrafish presented on computer screens placed on either side of the test tank. Immediately after the stimulus presentation, we dissected the subjects' brains and analyzed

their neurochemical profiles from whole brain extracts using high precision liquid chromatography (HPLC). We quantified the levels of dopamine, DOPAC (dopamine's metabolite), serotonin, and 5-HIAA (serotonin's metabolite) of socially isolated and control zebrafish. We also measured cortisol levels using salivary Cortisol Enzyme Immunoassays kits. We found that developmental social isolation altered dopamine neurotransmission, while social isolation in adulthood changed serotonin levels in the brain, findings that may represent an important distinction between development and maintenance of social behaviour. Additionally, social isolation also influenced the cortisol response to social stimulus presentation. We found adult isolation to reduce cortisol levels, a result that questions the optimal nature of high density group housing widely employed in zebrafish facilities. Acknowledgements: Supported by NSERC

Disclosures: S. Shams: None. **D. Chatterjee:** None. **R. Gerlai:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 616.01/U33

Topic: E.07. Food Intake and Energy Balance

Support: NIH Grant R037 DK35254 to TJB

Title: Reciprocal crosstalk between the sensory and sympathetic innervation of brown and white adipose tissue

Authors: *V. RYU[1,2], T. J. BARTNESS[1,2];
[1]Biol., Georgia State Univ., Atlanta, GA; [2]Obesity Reversal Ctr., Atlanta, GA

Abstract: Utilizing the sensory system (SS)-specific anterograde transneuronal tract tracer, the H129 strain of herpes simplex virus-1 and the fat pad sympathetic nervous system (SNS)-specific retrograde transneuronal tract tracer pseudorabies virus (PRV152), we previously demonstrated the neuroanatomical reality of the interscapular brown (IBAT) and inguinal white (IWAT) adipose tissue SS-SNS short and long feedback circuits. Functionally, we and others have shown that activation of IBAT and IWAT SNS innervation is the primary initiator of thermogenesis and lipolysis, respectively, with SS nerves responding to increases in IBAT and IWAT SNS drives. Therefore, we injected H129 intra-IBAT and PRV152 intra-IWAT as well as vice versa to define the extent of IBAT-SS/SNS and IWAT-SNS/SS communication centrally and peripherally. Surprisingly, we found H129+PRV152 colocalized neurons in the SNS ganglia

and DRG innervating IBAT/IWAT coupled with significant co-infections mostly related to IBAT-SS and IWAT-SNS feedback loops in multiple brain sites. These doubly-infected neurons imply short and long SS-SNS crosstalk between IBAT and IWAT. Demonstrative brain regions with the greatest representation of doubly-infected neurons were the nucleus of the solitary tract, intermediate and pontine reticular nuclei, periaqueductal gray, paraventricular hypothalamic nucleus, lateral hypothalamus and medial preoptic area. Collectively, our results strongly support the neuroanatomical fact of IBAT-SS/SNS and IWAT-SNS/SS short and long neural feedback circuits. In addition, prominent crosstalk between IBAT-SS and IWAT-SNS perhaps provides the neuroanatomical underpinnings for the interaction of IBAT-SS for the control of IWAT lipolysis as occur specifically with conditions of cold exposure, food restriction/deprivation, exercise and more generally with changes in adiposity.

Disclosures: V. Ryu: None. **T.J. Bartness:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: E.07. Food Intake and Energy Balance

Support: NIH R37DK35254

Title: Central glucoprivation rapidly stimulates lipolysis in some but not all white adipose tissue depots via the sympathetic nervous system

Authors: *L. A. SZYMANSKI[1], T. J. BARTNESS[2];
[1]Biol., [2]Biology, Ctr. for Obesity Reversal, Georgia State Univ., Atlanta, GA

Abstract: Tract tracing studies in our lab have identified neural pathways from the paraventricular hypothalamus to white and brown adipose tissue via hindbrain areas that have been implicated in the control of glucoprivic feeding and hyperglycemia in other rodents. It is likely that in Siberian hamsters these hindbrain neurons modulate the increases in sympathetic drive to white adipose tissue (WAT) after peripheral glucoprivic treatment. Hamsters treated with the glucoprivic agent 5-thio-D-glucose (5TG) show significantly greater rates of norepinephrine turnover (NETO) in epididymal (EWAT), retroperitoneal (RWAT), and mesenteric (MWAT) white adipose tissue compared to saline-treated hamsters. The current experiments test the hypothesis that central glucoprivation is sufficient to stimulate lipolysis in peripheral fat pads and confirm that increases in NETO to specific fat pads after 5TG treatment

correspond to increases in intracellular markers of increased lipolytic activity, specifically hormone-sensitive lipase (HSL) and phosphorylated HSL (pHSL). Adult hamsters received an injection of 50 nmoles of 5TG into the 4th ventricle (4V) and were sacrificed 15, 30, 60, and 210 minutes later. Inguinal white adipose tissue (IWAT), EWAT, RWAT, and MWAT were collected for measurement of HSL and pHSL using Western blot. Plasma concentrations of glucose, free fatty acids, and glycerol were measured at the time of sacrifice as further physiological measures of increased lipolysis. At 210 minutes after 5TG treatment there were no significant differences in the relative expression of pHSL/HSL in white adipose tissue, nor were there significant differences in plasma glucose, glycerol, and free fatty acids compared with saline treated animals, suggesting that the effects of central glucoprivation are acute and the animals had recovered after 3.5 h. At 30 min after 5TG treatment, when plasma glucose is significantly higher than saline-treated animals, preliminary results show an increase in the relative expression of pHSL/HSL in EWAT, supporting the idea that the increased sympathetic drive to EWAT seen in the previous experiment results in increased lipolytic activity. Preliminary results did not show increased relative expression of pHSL/HSL in IWAT 30 min after 5TG treatment, which also supports the previous results which showed no increases in NETO in IWAT after 5TG treatment. It is likely that glucose-sensing hindbrain neurons that have been identified as part of the pathway modulating sympathetic output to adipose tissue rapidly stimulate lipolysis in response to glucoprivation.

Disclosures: L.A. Szymanski: None. **T.J. Bartness:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

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VA merit

Title: Brain activation and inhibition in food intake and meal structures by abdominal surgery in mice

Authors: L. WANG[1], *Y. TACHE[2];
[1]UCLA, Los Angeles, CA; [2]UCLA Dep Med. Div. Digestive Dis, Los Angeles, CA

Abstract: There is still a lack of therapy to shorten recovery from postoperative ileus. Abdominal surgery inhibits food intake and gastric emptying (Stengel et al., AJP 2011), and induces c-Fos expression in the hypothalamic and medullary nuclei in rats (Bonas and Taché, Brain Res 1994; Wang et al., Brain Res 2011) indicative of activation of brain circuitries that may impact also on feeding behavior. In this study we mapped c-Fos in the brain, and assessed food intake and meal structures altered by abdominal surgery in mice. Male mice (C57BL/6) without access to food for 6-7 h received laparotomy and cecal palpation under isoflurane anesthesia 1-2 h before the dark phase. Controls remained in home cages. Brain sections were processed for c-Fos immunoreactivity (ir) 2 h post-surgery. For food intake monitoring and meal pattern analysis, mice were maintained in an automated episodic feeding monitoring system (BioDAQ, Research Diet Inc.). In control mice, there was moderate c-Fos-ir in the paraventricular nucleus (PVN), arcuate nucleus (Arc), and preoptic, lateral and dorsomedial areas of the hypothalamus, medial bed nucleus of stria terminalis (BST) and Edinger-westphal nucleus (E-W). Abdominal surgery increased Fos-ir in the prelimbic (119.1 ± 5.6 vs. 25.8 ± 5.0), insular (65.6 ± 7.6 vs. 10.2 ± 1.7) and cingulate (99.9 ± 6.5 vs. 29.4 ± 9.5) cortexes, nucleus of accumbens (82.2 ± 6.8 vs. 14.8 ± 4.7), lateral septum (133.5 ± 17.7 vs. 54.4 ± 4.4), BST (in ventral lateral subnucleus 69.9 ± 4.0 vs. 3.9 ± 1.6), supraoptic nuclei (100.3 ± 6.0 vs. 1.9 ± 0.8), PVN (214.8 ± vs. 101.1 ± 6.9), Arc (88.8 ± 7.9 vs. 30.1 ± 7.8), E-W (53.7 ± 2.7 vs. 22.7 ± 1.1), periaqueductal area (PAG) lateral area (49.5 ± 2.1 vs. 20.9 ± 2.1), external subnucleus of lateral parabrachial nucleus (95.0 ± 7.0 vs. 4.7 ± 1.2), locus ceruleus (75.0 ± 7.4 vs. 3.9 ± 0.4), Barrington's nucleus (36.7 ± 3.4 vs. 5.4 ± 0.7), A5 (data not shown), ventrolateral medulla (24.4 ± 2.7 vs. 1.1 ± 0.4), nucleus tractus solitarius (96.1 ± 8.0 vs. 5.6 ± 1.5) and area postrema (39.0 ± 4.1 vs. 7.0 ± 1.9). Abdominal surgery significantly reduced food intake assessed at 2, 4, 6, 12 and 24 h by 97-86% compared to controls. The meal structure analysis showed a significant reduction of feeding bouts, time spent on meals, and meal frequency and duration and size, prolonged intermeal interval and higher satiety ratio. Brain circuits of mice responsive to abdominal surgery include visceral regulatory centers, areas involved in pain and integrative nuclei related to stress, which may underlie visceral and behavioral alterations induced by abdominal surgery including inhibition of gastric emptying and food intake linked with increased satiation and satiety.

Disclosures: L. Wang: None. **Y. Tache:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 616.04/U36

Topic: E.07. Food Intake and Energy Balance

Support: CNPq

CAPES

Title: The blood-brain barrier regions in diet-induced obesity - dietary fats induce changes only in the medium eminence

Authors: A. F. S. RAMALHO[1], M. FIORAVANTE[1], J. MORARI[1], C. SOLON[1], N. R. V. DRAGANO[1], *A. L. OLIVEIRA[2], L. A. VELLOSO[1], E. P. ARAUJO[1];
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Abstract: Hypothalamic inflammation and dysfunction are induced by dietary fats and play an important pathophysiological role in experimental obesity. Histological and molecular studies have failed to demonstrate an inflammatory action of dietary fats in regions other than the hypothalamus. This raises the possibility that dietary fats may disturb the blood-brain barrier (BBB) specifically in the hypothalamus. To investigate this hypothesis we used microdissection to prepare RNA from samples collected from the main BBB regions; medium eminence (ME), vascular organ of the terminal lamina (OVLT), subcommissural organ (SCO) and subfornical organ (SFO). Hippocampus was used as a control region. Real-time PCR revealed that after seven days on a high-fat diet, only ME presented increased expression of the inflammatory cytokine TNFa. The tanycyte marker GLAST underwent significant increase only in ME and OVLT. Confocal imaging staining for the tanycyte markers IGFBP2 and caveolin-1 showed an early disorganization of the alignment of cells in the limit of the ME which was confirmed by transmission electron microscopy. There were no changes in the distribution and organization of IGFBP2 and caveolin-1 positive cells in the other regions of the BBB. On time-course experiments we observed that the expression of at least two markers of tanycytes, caveolin-1 and GLUT1 are reduced after two weeks feeding on a high-fat diet, which is accompanied by a reduction of the hypothalamic expression of inflammatory cytokines. After four weeks on high-fat diet the tanycytes are detected irregularly distributed within the arcuate nucleus. We hypothesized that changes in the local expression of neurotrophic factors could be involved in the abnormalities of the tanycyte distribution and marker expression. In fact, BDNF expression was increased after one week on high-fat diet but reduced after two weeks. Confocal microscopy showed that in lean mice BDNF was predominantly present outside the cells in the transition between the ME and the arcuate nucleus, whereas in mice fed on the high-fat diet for two weeks it was present within the tanycytes. The immunoneutralization of BDNF resulted in reduced hypothalamic expression of the anti-inflammatory cytokines IL10 and IL6. In conclusion, dietary fats act specifically in the ME to promote tanycyte disorganization and induction of inflammatory markers. BDNF emerges as a neutrophic factor potentially involved in this regulation.

Disclosures: **A.F.S. Ramalho:** None. **M. Fioravante:** None. **J. Morari:** None. **C. Solon:** None. **N.R.V. Dragano:** None. **A.L. Oliveira:** None. **L.A. Velloso:** None. **E.P. Araujo:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

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Topic: E.07. Food Intake and Energy Balance

Support: Colorado College Research and Development Grant

Colorado College Venture Grant

Title: Developmental exposure to PBDE flame retardants induces hypothyroidism and impacts hedonic tone in adult rats

Authors: ***L. L. DRISCOLL**[1], J. WATTS[2], R. KASEMODEL[2], T. TUMMINO[2], W. HARRIS[2], R. LACH[2];
[1]Colorado Col., Colorado Spgs, CO; [2]Colorado Col., Colorado Springs, CO

Abstract: Although they are no longer used in the manufacture of new products, polybrominated diphenyl ethers (PBDEs) are ubiquitous in the environment, and they bioaccumulate in wildlife and humans, especially in the United States. In humans, the highest levels are found in breastfed infants and small children, which has implications for brain development. Previously, we have found that when rat pups are exposed to the US-produced PBDE commercial mixture DE-71, thyroid hormone (especially thyroxine or T4) levels are dramatically suppressed. Behaviorally, exposed animals demonstrate mild learning deficits, and female rats demonstrate motivational impairments later in life. Exposed female rats also voluntarily consume more sucrose water than do non-exposed rats of both sexes. In the current study, male and female rats exposed to 30 or 60 mg/kg/day DE-71 on postnatal days 6-12 had suppressed serum T4 levels as pups. As adults, the higher dose female rats voluntarily consumed more ethanol than did exposed males or controls. In contrast, there were no treatment differences in anxiety levels or responses to a pentobarbital challenge in the open field. These results, paired with the finding that this same treatment group demonstrates increased sucrose consumption and decreased motivation to complete cognitive tasks, suggests that particularly in females, early exposure to DE-71 can influence hedonic tone in adulthood. It is important to recognize that these types of motivational disruptions can inaccurately manifest themselves as cognitive deficits in appetitively motivated tasks.

Disclosures: **L.L. Driscoll:** None. **J. Watts:** None. **R. Kasemodel:** None. **T. Tummino:** None. **W. Harris:** None. **R. Lach:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

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Support: IN224314 from DGAPA-UNAM to OPG supported this work.

Title: Potential glutamatergic and endocannabinergic interaction regulates food intake

Authors: ***A. SANCHEZ-FUENTES**, A. L. BECERRIL MELÉNDEZ, A. ROMANO LÓPEZ, O. AMANCIO BELMONT, M. MÉNDEZ DÍAZ, A. E. RUIZ CONTRERAS, O. PROSPÉRO GARCÍA;
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Abstract: The endocannabinoid and glutamatergic systems have been involved in the regulation of food intake (FI) and energy balance (EB). The hypothalamus regulates both processes FI and EB integrating information from peripheral tissues. Glutamate release in the lateral hypothalamus (LH) seems to be a main signal to induce food intake via mGlu5R. mGlu5R mechanism to enhance food intake is not completely understood. In this context, we decided to examine pharmacologically the potential modifications of mGlu5R stimulation on food intake when DGL activity was hampered or the CB1 was blockaded. Wistar albino male rats received LH injections into the LH, by using a within-subjects Latin-square design with vehicle, (RS)-2-Chloro-5-hidroxyphenylglycine (CHPG, 5.6 μg; selective agonist of mGlu5r), Tetrahydrolipstatin (THL, 1.2 μg; DGL inhibitor), AM251 (CB1 antagonist) and a combination of them. We found that the activation of mGlu5rs significantly increased ($P<0.05$) the total food intake during the first four hours after injection, but markedly during the first hour. AM251 or THL blocked this effect. Taken together, these results suggest a potential interaction of the endocannabinoid and glutamatergic systems to regulate food intake. It seems like 2-AG is the endocannabinoid resulting from the activation of mGlu5rs in the LH. In conclusion we believe glutamate via mGlu5R promotes 2-AG synthesis and release in the LH thereby inducing food intake.

Disclosures: **A. Sanchez-Fuentes:** None. **A.L. Becerril Meléndez:** None. **A. Romano López:** None. **O. Amancio Belmont:** None. **M. Méndez Díaz:** None. **A.E. Ruiz Contreras:** None. **O. Prospéro García:** None.

Poster

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Topic: E.07. Food Intake and Energy Balance

Support: DK104897

Title: Neuroanatomical evidence for neurohumoral transmission by melanin-concentrating hormone neurons in the rat

Authors: V. R. KONANUR, T. M. HSU, *S. E. KANOSKI, J. D. HAHN;
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Abstract: Melanin-concentrating hormone (MCH) is a cyclic 19 amino acid peptide with diverse biological functions. The role of neuronal MCH ranges from the regulation of energy homeostasis to the control of sleep and fundamental behaviors. The majority of MCH-expressing somata are restricted to five regions of the lateral hypothalamic area (LHA), and the zona incerta (ZI) (Hahn, J. D. 2010). However, MCH neuron axons are distributed widely, and reach multiple brain regions. Here we investigated a novel non-synaptic route whereby MCH of hypothalamic or ZI origin could reach distant neural targets, by volume transmission via the ventricular system. The neural tracer cholera toxin B subunit (CTB) was injected unilaterally into the lateral ventricle of male rats. Dual immunofluorescent detection of CTB and MCH was then performed to visualize CTB-containing and MCH-expressing somata. Initial observations revealed abundant retrograde labeling within the hypothalamus and ZI, and numerous instances of colabeled neurons. Subsequent analysis of an experimental dataset (restricted to the side of the brain contralateral to the injection side) found that out of 660 MCH somata (in the ZI and hypothalamus), approximately a third (216 = 32.7%) colocalized CTB; this represented 43.8 % of CTB-containing somata counted within the lateral hypothalamic zone and ZI. Somata colocalizing MCH and CTB were present in the ZI and in 13 regions of the lateral hypothalamic zone; however, about two-thirds (69%) of colabeling was restricted to just three regions: The ZI (37.5%), the LHA dorsal region (LHAd; 17.6%), and LHA juxtadorsomedial region (LHAjd; 13.8%). It is also noteworthy that colabeling was comparatively low in the LHA ventral region medial zone (LHAvm; 6.4 %) and the LHA magnocellular nucleus (LHAm; 2.8 %)_two regions

found here (and shown previously) to contain abundant MCH somata. Additional immunofluorescent analysis at confocal microscopic resolution revealed close appositions of synaptophysin- and MCH-expressing axon terminals with laterally-extending branches of vimentin-expressing ependymal cells at the level of the third ventricle (presumptive tanycytes). Furthermore, high-sensitivity enzyme-linked immunosorbent assay indicated the presence of MCH in the cerebrospinal fluid of rats under physiological (untreated) conditions. Collectively, these data suggest MCH-expressing neurons within the ZI and/or LHA release MCH into the ventricular system to activate MCH-responsive neurons via a neurohumoral route, and the extent to which this occurs varies between MCH neuron subpopulations.

Disclosures: **V.R. Konanur:** None. **T.M. Hsu:** None. **S.E. Kanoski:** None. **J.D. Hahn:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

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HHMI PERSIST Education Grant

Title: Hypothalamic chemoarchitecture in the adult male rat: Creating canonical atlas maps for co-visualized immunoreactive peptidergic neuronal populations (α-MSH, nNOS, MCH) and their fiber systems in multiple brains

Authors: *C. E. WELLS[1], A. ACOSTA[2], D. ALDRETE[2], A. CARRION[2], L. CASTRO[2], A. C. ESCAPITA[2], E. ESPINOZA[2], K. DE LA FUENTE[2], A. GARRETT[2], A. GOMEZ[2], N. GOMEZ[2], C. HERNANDEZ-CASNER[2], M. LUEVANO[2], A. LOPEZ[2], D. MARTINEZ[2], E. MENDOZA[2], M. ORTEGA[2], M. PEREZ[2], E. RANGEL[2], E. REZA[2], J. RIVERA[2], C. ROMAN[2], A. ROSAS[2], C. SEADE-GALINDO[2], J. TERAN[2], J. UNPINGCO[2], S. VALDEZ[2], A. M. KHAN[3];
[1]Biol. Sci., [2]Biol. Sciences, HHMI PERSIST Program: Brain Mapping & Connectomics Track, [3]Biol. Sci. and UTEP Systems Neurosci. Lab., The Univ. of Texas at El Paso, El Paso, TX

Abstract: While the hypothalamus is a major homeostatic control center and its functions have been extensively studied, the precise circuitry underlying many of these functions remains undescribed. We have begun to remedy this situation by contributing to a chemoarchitectural

atlas of the rat hypothalamus, based upon the Swanson reference atlas of the rat brain. Here we expand our previous reporting of the distribution of and interactions among α-melanocyte stimulating hormone (α-MSH), melanin-concentrating hormone (MCH), and neuronal nitric oxide synthase (nNOS) in the adult male rat, to include data from multiple brains. To do so, we have recruited a cohort of freshmen undergraduates and taught them formal atlas-mapping techniques within an HHMI-funded laboratory based course: Brain Mapping & Connectomics. Working in groups, they have completed comprehensive sets of maps based upon five additional brains. This has allowed expression patterns for α-MSH, MCH, and nNOS to be compared across brains, and individual variability to be assessed. While there is some variation in the density of fibers in many regions, the overall patterns are markedly consistent between brains, although there are some exceptions for individual animals (for example, case K10-053 has drastically increased MCH expression surrounding the 3rd ventricle versus other brains studied). This work marks the first time that the anatomical distributions of α-MSH, MCH, and nNOS have been mapped together in the hypothalamus with such detail and, to our knowledge, the first time that freshmen have contributed to chemoarchitectural brain atlas development as part of a teaching lab. The chemoarchitectural atlas will aid in experimental design and data interpretation for investigators studying the functionality of the rat hypothalamus.

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Poster

616. Food Intake and Energy Balance: Anatomy and Development

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Support: NIH Grant GM109817

Title: Distribution and chemical identification of neurons projecting to the ventral tegmental area: a combined retrograde tracing and immunohistochemical study in the adult male rat, with special reference to the lateral hypothalamic area

Authors: *E. M. WALKER[1], B. DE HARO[2], R. H. THOMPSON[3], A. M. KHAN[2];
[1]Biol. Sci., [2]Biol. Sci. and UTEP Systems Neurosci. Lab., Univ. of Texas El Paso, El Paso, TX;
[3]Biol. Sci., USC, Los Angeles, CA

Abstract: The lateral hypothalamic (LHA) and ventral tegmental (VTA) areas help orchestrate motor behaviors related to feeding. Diencephalic-derived hypocretin 1/orexin A (H/O) and melanin-concentrating hormone (MCH) are implicated in the control of ingestive behaviors and arousal and send their projections to the VTA. However, it is unclear how these peptidergic neurons contribute to the precise connectivity between the LHA and VTA. We performed bilateral injections into the VTA of 43 male rats; each injection delivered either the retrograde tracers FluoroGold (2%; FG) or cholera toxin subunit b (CTb). We characterized the injection sites in two representative cases (one FG and one CTb) and mapped the back-filled cell bodies to the Swanson rat brain atlas (Brain Maps, 3rd edition, 2004). We also used immunohistochemistry to double-label the traced neurons using antibodies targeting CTb and either H/O (FG case) or MCH (CTb case), in order to examine the spatial arrangement of H/O+ and MCH+ cell bodies projecting to the VTA. We found that the injection sites mapped to Swanson atlas levels 36 (FG) and 38 (CTb), within the middle portion of the VTA. Tracer-filled neurons were found in several forebrain and hindbrain locations, including the prefrontal cortex, nucleus accumbens, lateral septum, discrete LHA subdivisions, the lateral habenula and the lateral part of the parabrachial nucleus. In all regions, most of the labeled neurons were located primarily ipsilateral to the injection site. For both injection cases, the nucleus accumbens and lateral septum contained the greatest number of back-filled cells, and the parabrachial nucleus and lateral habenula the least. Some CTb+ neurons were immunostained for calbindin, particularly around the anterior commissure. FG+ cells were found in the deep layers of the medial prefrontal cortex, but similar labeling was not seen for CTb labeled cells. A few of the traced neurons found in the suprafornical LHA (LHAs) expressed H/O, whereas a few of the traced cells found in the dorsal LHA expressed MCH. Our data confirm previous findings that some LHA neurons projecting to the VTA express H/O and MCH, and extend them by providing information about the precise subdivisions within the LHA that harbor these neurons. They also build on previous work by demonstrating that efferent projections to the VTA from specific LHA subdivisions are peptidergic. From the initial characterization of the injection cases we have made thus far, it is apparent that discrete parts of the VTA receive an integrated series of inputs from neuronal populations widely distributed in the brain, and that the LHA provides an important contribution to this afferent information.

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Poster

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Topic: E.07. Food Intake and Energy Balance

Support: NIH Grant GM109817

Title: Connections of the rostral portion of the hypothalamic arcuate nucleus: A combined anterograde and retrograde study in the adult male rat

Authors: *A. MARTINEZ[1], B. E. PINALES[2], A. M. KHAN[2];
[1]Biol. Sci., [2]Biol. Sci. and UTEP Systems Neurosci. Lab., Univ. of Texas At El Paso, El Paso, TX

Abstract: The arcuate nucleus (ARH) is an important periventricular neuroendocrine structure and also serves as an active sentinel of metabolic state, contributing critically to the regulation of energy balance. While ARH function has been intensively investigated, a complete understanding of ARH neuronal connections to and from larger network targets remains poorly understood. To address this knowledge gap, we performed neuroanatomical tract tracing using a cocktail injection of anterograde and retrograde tracers. Specifically, cholera toxin subunit b (CTb) and Phaseolus vulgaris leucoagglutinin (PHA-L) were co-administered into the rostral ARH of adult male Sprague Dawley rats. To visualize tracer staining, immunohistochemical techniques were applied and the sections imaged at high resolution using wide-field microscopy. Using an adjacent Nissl-stained tissue series as a guide, both cell bodies sending projections to the ARH, and axons projecting from ARH neurons were mapped to the Swanson rat brain atlas (Brain Maps, 3rd edition, 2004). ARH-projecting regions (Swanson nomenclature), marked by CTb-filled cell bodies, included the ORBv, TTd layer 4, ILA layer 6a, LSi, LSd, LSv, CLA, ACB, BST(ad, dm, pr,v), ZI, LPO, MEPO, MPO, MPN(m, c, l), ADP, PS, AHA, SCH, RCH, PVHap, pv, LHA, MEAad, MEApd, CEAm, VMH, and PMv. Regions receiving ARH innervation as determined through PHA-L fiber staining included (again, Swanson nomenclature): the LSv, LS, ACB, BST(ad, dm, pr, v), ZI, LPO, MEPO, MPO, MPN, AVPV, AV, PS, AHA, AHN, PSCH, PT, SI, SON, PVT, DMH, VMH, ME, PH, PVp, and PMv. Initial mapping results have confirmed ARH connectivity previously described. They have also identified new patterns not previously documented elsewhere, including general trends of reciprocal connectivity for nuclei sending or receiving ARH innervation. Rostral ARH afferents and efferents appear to travel ipsilaterally to and from the nucleus, respectively, since we observed minimal CTb and PHA-L immunoreactivity contralateral to the injection site. With our rostral ARH injection site, we also observed sparse cell body and fiber staining in midbrain regions. In combination with other data, these data may be indicative of possible rostrocaudal differences for arcuate neuron projections and afferents. In summary, this study closely examines

rostral ARH forebrain afferents and efferents through high resolution mapping of CTb-ir perikarya and PHA-L axons to the Swanson rat brain atlas. The data provide detailed information about how the ARH is connected to the rest of the forebrain to form the networks relevant for the regulation of energy homeostasis.

Disclosures: **A. Martinez:** None. **B.E. Pinales:** None. **A.M. Khan:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

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Topic: E.07. Food Intake and Energy Balance

Support: NIDA-IRP, NIH

Title: Behavior-associated and post-consumption glucose entry into the nucleus accumbens extracellular space during glucose free-drinking in trained rats

Authors: *K. T. WAKABAYASHI, E. A. KIYATKIN;
Behavioral Neurosci. Br., NIH/NIDA, Baltimore, MD

Abstract: Glucose is the primary energetic substrate for the metabolic activity of brain cells and its proper delivery from the arterial blood is essential for neural activity and normal brain functions. Glucose is also a unique natural reinforcer, supporting glucose-drinking behavior without food or water deprivation. While it is known that glucose enters brain tissue via gradient-dependent facilitated diffusion, it remains unclear how glucose levels are changed during natural behavior and whether the direct central action of ingested glucose can be involved in regulating glucose-drinking behavior. Here, we used glucose biosensors with high-speed amperometry to examine the pattern of phasic and tonic changes in extracellular glucose in the nucleus accumbens (NAc) during unrestricted glucose-drinking in well-trained rats. We found that the drinking behavior is highly cyclic and is associated with relatively large and prolonged increases in extracellular glucose levels. These increases had two distinct components: a highly phasic but relatively small behavior-related rise and a larger tonic elevation that results from the arrival of consumed glucose into the brain's extracellular space. The large post-ingestion increases in NAc glucose began minutes after the cessation of drinking and were consistently associated with periods of non-drinking, suggesting that the central action of ingested glucose could inhibit drinking behavior by inducing a pause in activity between repeated drinking bouts. Finally, the difference in NAc glucose responses found between active, behavior-mediated and passive

glucose delivery via an intra-gastric catheter confirms that motivated behavior is also associated with metabolic glucose use by brain cells. Supported by NIDA-IRP.

Disclosures: K.T. Wakabayashi: None. **E.A. Kiyatkin:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

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Topic: E.07. Food Intake and Energy Balance

Support: NIH RO1 DK089237

Title: Leptin suppresses development of GLP-1 innervation to the paraventricular nucleus of the hypothalamus

Authors: *J. E. BIDDINGER[1,3], R. B. SIMERLY[3,2];
[1]Developmental Neurosci., [2]Children's Hosp. Los Angeles, Los Angeles, CA; [3]USC, Los Angeles, CA

Abstract: The nucleus of the solitary tract (NTS) receives and integrates visceral nutritional status, and primarily sends this information to the hypothalamus to coordinate energy balance and neuroendocrine responses. Leptin acts directly on NTS neurons to regulate food intake and energy expenditure. In addition to leptin's role in satiety signaling, it also functions as a neurotrophic factor during development, as leptin is required for normal axon outgrowth from the arcuate nucleus of the hypothalamus to the paraventricular nucleus of the hypothalamus (PVH). Given the importance of leptin signaling in the regulation of ingestive behavior, and leptin's previously identified role in specifying patterns of innervation within the hypothalamus, we tested if leptin is required for development of neuronal projections from the NTS to the hypothalamus. The projections of NTS neurons that express leptin receptors (LepRb) were visualized by injecting an AAV virus into the NTS of LepRb-cre mice that resulted in cre-dependent GFP axonal labeling. The PVH contained a dense plexus of labeled axons in these mice, indicating that the PVH is a primary target of NTS LepRb-expressing neurons. Using immunohistochemistry, we identified GLP-1 as the predominant neurochemical phenotype of LepRb-expressing neurons in the NTS: 70% of GLP-1 neurons co-express leptin receptors at postnatal (P) day 16, and 100% of these neurons are responsive to leptin at this time as determined by leptin-induced pSTAT3 immunoreactivity. In neonatal mice, GLP-1 axons reach the PVH between P6 and P10, which is coincident with an early postnatal surge in leptin levels.

Compared with wild-type mice, GLP-1 fiber density is significantly greater in the PVH of leptin-deficient *Lep*$^{ob/ob}$ mice at P16, a difference that persists into adulthood, with no change in GLP-1 neuron number in the NTS. These results suggest that leptin acts directly at the level of the NTS to inhibit development of neural projections conveying leptin-sensitive, visceral sensory information to the PVH, which may contribute to sustained dysregulation of food intake and energy expenditure.

Disclosures: J.E. Biddinger: None. **R.B. Simerly:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

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Support: OPKO Health

Title: Central inhibition of c-jun n-terminal kinase suppresses feeding and reduces body weight

Authors: *P. LOGRASSO, S. GAO;
Scripps Res. Inst., Jupiter, FL

Abstract: The role for c-Jun N-terminal Kinase (JNK) in the regulation of energy homeostasis is not well understood especially as it relates to the role for individual JNK isoforms and mechanism of action. To investigate this we explored the role for JNK in the control of food intake and body weight by utilizing of a series of highly selective JNK inhibitors. SR-3306 is a potent JNK1/2/3 (pan JNK) inhibitor with good brain penetration. SR-4073 is a potent JNK1/2/3 (pan JNK) inhibitor with poor brain penetration. Our preliminary data utilizing SR-3306, and its structurally similar non-brain penetrant counterpart SR-4073, suggests feeding behavior was controlled centrally by JNK and not peripherally. Use of SR-3306 in *Jnk1* and *Jnk2* knockout mice support the notion that neither JNK1 nor JNK2 was crucial for feeding control. The reduction of food intake was accompanied by decreases in body weight. A pair-feeding study further showed that the weight loss effect was entirely accounted for by reduced food intake. Importantly, the conditioned taste aversion test showed that the anorectic action following SR-3306 treatment was not due to compound toxicity. The potential central actions of JNK were also assessed. Similar to the findings by systemic treatment, a bolus intracerebroventricular (i.c.v.) injection of the compound reduced food intake and body weight. Thus, the activity of JNK in the CNS appeared to mediate the anorectic actions of JNK inhibition. We also assessed the effects of

SR-3306 on mice fed with 60% kcal fat diet (high-fat diet). Daily i.p. injection of the compound (30mg/kg) for 8 days decreased high-fat diet intake, and markedly reduced body weight gain and fat mass. In addition, JNK inhibition improved leptin sensitivity in DIO mice suggesting that JNK may exert its anorectic effects through the leptin pathway. Collectively, the data demonstrate that central inhibition of JNK activity exerts an anorectic effect and reduces body weight and implicates JNK in the regulation of body weight homeostasis.

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Poster

616. Food Intake and Energy Balance: Anatomy and Development

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Support: NIH Grant GM109817

Title: Initial chemoarchitectural and connectional characterization of polymodal association cortical structures with the diencephalon: Immunohistochemical and tract tracing studies

Authors: ***K. NEGISHI**[1], J. HAMDAN[2], A. M. KHAN[2];
[2]Biol. Sci. and UTEP Systems Neurosci. Lab., [1]UNIVERSITY OF TEXAS AT EL PASO, El Paso, TX

Abstract: Polymodal association cortical structures (CTSpm) located in the medial prefrontal region of the brain, including the anterior cingulate area (ACA) and prelimbic areas (PL), have been associated with a multitude of functions. CTSpm structures are well known for their roles in attention, working memory, and goal-directed behaviors. Recent efforts have emphasized a role for various CTSpm, in conjunction with visceral sensory-motor areas such as the infralimbic area (ILA), in reward-risk appraisal, the extinction of learned behaviors and induced feeding under sated states. These diverse functions are ostensibly constrained by the underlying anatomy and connectivity of various CTSpm structures, which have known connections to a variety of thalamic and hypothalamic cell populations. It is therefore worthwhile to establish clear ACA and PL connectional relations across their rostrocaudal extent using combined anterograde and retrograde tracer injections targeting these regions. Although CTSpm connections have been

previously reported, their precise distributions throughout diencephalic structures have not been completely elaborated. Here, we examine CTSpm networks using the cytoarchitectonic criteria and nomenclature of the Swanson atlas of the rat brain (2004). Initial tracer injections of the anterograde and retrograde tracers, PHA-L and CTb, respectively, were centered primarily within the dorsal part of the anterior cingulate cortex (ACAd) or the rostral PL. For these cases, both PHA-L fibers and CTb-filled cell bodies were mainly focused in the lateral part of the mediodorsal nucleus, paratenial nucleus, zona incerta, basolateral amygdala, claustrum, and the primary motor cortex. These results are consistent with previous reports (Coolen et al., 2006; Sesack et al., 1989). Lighter distributions of PHA-L fibers were also observed in midline thalamic structures including the paraventricular, central medial and to a lesser extent, the nucleus reuniens. ACAd projections were notably sparse within the hypothalamus. In addition to cytoarchitectonic boundaries, diencephalic structures were further distinguishable by chemically defined cell populations. Our approach allows us to navigate these diverse and often overlapping cell groups using immunocytochemistry. These findings will inform functional investigations using cell type-specific methods such as optogenetics or DREADD technology.

Disclosures: **K. Negishi:** None. **J. Hamdan:** None. **A.M. Khan:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 616.15/V5

Topic: E.07. Food Intake and Energy Balance

Title: Contribution of D1 and D2 type neurons to nucleus accumbens efferent pathways and their influence on feeding

Authors: ***C. W. BOND**[1], K. E. FURMAN[1], B. B. LAND[2], D. OTTENHEIMER[1], R. J. DILEONE[1];
[1]Yale Univ., New Haven, CT; [2]Univ. of Washington, Seattle, WA

Abstract: The nucleus accumbens (NAc) is a basal ganglia structure critically important for reward learning and food seeking. The NAc is primarily composed of two distinct populations of medium spiny neurons (MSNs), expressing either D1 or D2-type dopamine receptors, with differential roles in reward learning and feeding behavior. The lateral hypothalamus (LH) and ventral pallidum (VP) are two prominent target sites of the NAc MSNs. We sought to describe the composition of these projections in more detail in the mouse and to assess their activity and influence during feeding behavior. Using retrograde tracing of LH-projecting D1 and D2

neurons, we find that the LH pathway is predominantly composed of D1 expressing neurons. Anterograde viral labeling of D1 and D2 specific efferents shows results consistent with this finding. To assess the activity of LH-projecting D1 and D2 neurons, food-restricted animals injected with a retrograde tracer, Fluorogold were re-fed for 90 minutes. Neural activity during re-feeding was determined by cFos expression. We find that few LH-projecting MSNs are cFos+ during re-feeding, with only 12% of Fluorogold labeled cells activated. Moreover, 89% of active Fluorogold labeled cells express the D1 receptor, consistent with the predominant anatomical composition. These anatomical and activity assessment studies, together with functional manipulation of D1 and D2 pathways, better describe how the NAc controls feeding.

Disclosures: C.W. Bond: None. **K.E. Furman:** None. **B.B. Land:** None. **D. Ottenheimer:** None. **R.J. DiLeone:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: E.07. Food Intake and Energy Balance

Support: NIH Grant DK089237

TSRI RCDF

Title: Leptin promotes the development of oxytocin projections from the paraventricular hypothalamic nucleus to the dorsal vagal complex

Authors: *A. ELSON[1], R. SIMERLY[2];
[1]Anat. and Neurobio., [2]Developmental Neurosci., Children's Hosp. Los Angeles, Los Angeles, CA

Abstract: The paraventricular nucleus of the hypothalamus (PVH) contains multiple cell types that respond to varied internal and external signals and integrates this information to coordinate autonomic responses. Descending projections from the PVH to the dorsal vagal complex (DVC) represent a key pathway for autonomic regulation and Oxytocin (Oxy) neurons have an established role in the DVC as a modulator of autonomic processes. During development, leptin functions to direct targeting of axons from the arcuate nucleus of the hypothalamus (ARH) to the PVH and here we confirmed that inputs onto Oxy neurons in the PVH from AgRP neurons in the ARH are reduced in leptin-deficient *Lep*$^{ob/ob}$ mice. However, it is unknown if leptin is required

for the development of downstream projections to the DVC. We used Oxy Receptor-Venus mice to confirm expression of the Oxy receptor in the nucleus of the solitary tract (NTS) and dorsal motor nucleus of the vagus nerve (DMX), the sensory and motor components of the DVC, respectively. To determine if leptin is required for the development of Oxy projections from the PVH to the DVC, we used a genetically targeted axonal marker to visualize projections of Oxy neurons in leptin-deficient $Lep^{ob/ob}$ mice. The density of projections from PVH Oxy neurons to the NTS were markedly reduced in $Lep^{ob/ob}$ mice on postnatal day 16, prior to the onset of obesity, yet there was no change in the number of Oxy neurons in the PVH. Because they lack leptin receptors, the developmental actions of leptin on Oxy neurons are likely due to indirect influences that are dependent on innervation by leptin-sensitive neurons such as those in the ARH, or possibly through target-derived mechanisms that result from developmental actions of leptin on NTS neurons. By exerting lasting effects on the architecture of descending hypothalamic pathways, perturbations in leptin signaling during development may contribute to autonomic dysfunction.

Disclosures: **A. Elson:** None. **R. Simerly:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 616.17/V7

Topic: E.07. Food Intake and Energy Balance

Support: NIH Grant 1R01DK102918

Title: Electric remodeling of AgRP and POMC neurons is driven by diet composition and precedes weight gain and leptin insensitivity

Authors: ***J. GAMMONS**, W. WEI, D. SUTHERLAND, A. SMITH, C. KACZOROWSKI, K. O'CONNELL;
Physiol. and Biophysics, Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: Obesity leads to chronic metabolic disruption and continues to be a rising epidemic. Centrally projecting neurons from the arcuate nucleus of the hypothalamus (ARH) regulate feeding behavior and demonstrate altered biophysical properties in response to long term consumption of a high-fat diet (HFD). Hypothalamic leptin insensitivity develops as a result of chronic HFD, however this is preceded by persistent, unregulated firing of AgRP/NPY neurons that regulate appetite, thus leading to increased food intake. To investigate the impact of short-

term HFD consumption on neuronal excitability, mice were fed HFD ad libitum for up to 6 days and spontaneous firing from AgRP/NPY neurons in acute brain slices measured. This brief HFD consumption resulted in a significant increase in AgRP neuronal spiking to a rate nearly identical to long-term HFD-fed mice. Remarkably, we found that 100 nM leptin still robustly inhibited AgRP/NPY firing in short-term HFD-fed mice, thus the increased excitability of AgRP neurons is not a consequence of leptin-insensitivity. To determine the role of diet composition versus calorie consumption, mice were pair-fed high-fat diet (HFD-CR) yoked to an age-matched control group fed a low-fat diet (LFD). HFD-CR mice gained significant weight compared to the LFD group and AgRP neurons from HFD-CR mice exhibited increased spiking nearly identical to mice fed ad libitum, suggesting that diet composition may be more important than calorie intake for modulating the intrinsic excitability of arcuate AgRP/NPY neurons. POMC/CART neurons reduce feeding behavior when activated by endogenous hormones such as leptin and are regulated by AgRP/NPY neurons, but the intrinsic and synaptic excitability, as well as effects of leptin resistance, have yet to be determined. In order to discriminate between the roles of POMC and AgRP neurons on energy homeostasis and the impact on neuronal excitability through circulating hormones, POMC-GFP mice fed HFD will be used for acute brain slice recording of both intrinsic and synaptic excitability. Remodeling of the feeding circuitry within the hypothalamus will also be investigated using immunohistochemical techniques. As the effect of caloric intake appears to be outweighed by the content of diet on AgRP firing, we postulate the same will apply to POMC neurons. We will also determine whether HFD directly alters POMC neuronal excitability or if changes in POMC neuronal activity occur secondary to the response of AgRP neurons to HFD.

Disclosures: J. Gammons: None. **W. Wei:** None. **D. Sutherland:** None. **A. Smith:** None. **C. Kaczorowski:** None. **K. O'Connell:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 616.18/V8

Topic: E.07. Food Intake and Energy Balance

Title: Neuroanatomical characterization of bombesin receptor subtype 3 (brs-3) neurons using brs3-t2a-cre-er^{t2} mice

Authors: *S. H. ZAHLER, C. XIAO, R. A. PINOL, M. L. REITMAN;
DEOB, NIDDK, Natl. Inst. of Hlth., Bethesda, MD

Abstract: Introduction: Bombesin receptor subtype 3 (BRS-3) is an orphan G-coupled-protein receptor. BRS3 is expressed largely in the central nervous system and is involved in the regulation of body temperature, food intake, and heart rate. We now report a mouse line that produces tamoxifen-regulated Cre in cells expressing Brs3. Methods: Brs3-T2A-CreER^{T2}mice were produced by homologous recombination into the native genomic Brs3 locus. Brs3-T2A-CreER^{T2} and Ai9 mice (carrying a Cre-activated tdTomato reporter) were bred, and the progeny were treated with tamoxifen to express the fluorescent reporter. Results: Dense tdTomato fluorescence in neurons was observed in the following hypothalamic regions: preoptic area (POA), paraventricular nucleus of the hypothalamic (PVH), dorsomedial hypothalamus (DMH), and bed nucleus of the stria terminalis (BNST). High expression was also present in the medial amygdala (MeA) and parabrachial nucleus (PBN). Dense fibers were observed in the dorsal raphe nucleus (DR), nucleus of the solitary tract (NTS), ventral tegmental area (VTA), and periaqueductal gray (PAG). The Cre expression pattern is consistent with that previously reported for Brs3 using mRNA *in situ* hybridization and ligand binding. Conclusions: The BRS3-T2A-CreER^{T2} mice faithfully express Cre in Brs3 neurons, including multiple hypothalamic nuclei. The availability of this mouse will facilitate neuroanatomical and physiological studies of Brs3.

Disclosures: **S.H. Zahler:** None. **C. Xiao:** None. **R.A. Pinol:** None. **M.L. Reitman:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

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Topic: E.07. Food Intake and Energy Balance

Support: FONDECYT Grant 1140477

CMA BIO BIO, CONICYT Grant ECM-12

Title: Structural changes induced for acute hyperglycemia in median eminence tanycytes and vasculature

Authors: *F. A. MARTINEZ ACUÑA[1], M. CIFUENTES[2], K. SALAZAR[1], N. JARA[1], F. NUALART[1];
[1]Dept. de Biologia Celular, Facultad de Cs Biológicas., Univ. of Concepcion, Concepcion, Chile; [2]Univ. of Malaga, Malaga, Spain

Abstract: The median eminence (ME) is located in the basal region of the third ventricle of the brain. The ME contains blood vessels lacking a blood-brain barrier, thus allowing the diffusion of glucose from the blood into brain tissue. The transfer of glucose is also limited by a second barrier (EM-CSF) formed by specialized glial cells, the beta-2 tanycytes. Structural modifications of these cells could regulate the passage of glucose to the CSF in order to stimulate glucosensing. We evaluated the effect of hyperglycemia on the cell architecture and vascularization of the ME. We used intraperitoneal injections of glucose to generate hyperglycemia in Wistar rats; these were sacrificed 30 min after injection. The brain tissue was dissected for confocal spectral microscopy (multilabeling and 3D reconstruction) and electron microscopy analysis (TEM). Using 1µm and 40µm brain sections, we evaluated vimentin and GFAP expression in glial cells as well as changes in the blood vessel structure. 3D-imaging was performed by Z-stack microscopy and analyses were rendered using Imaris software. Furthermore, ultrastructural studies were performed using TEM. We confirmed the presence of blood vessels unrestricted by a barrier in the ME. Hyperglycemia produced a significant increase in the arborization of glial cells in this region. Electron microscopy showed beta-2 tanycytes hyperplasia, increased peri-capillary spaces, and more vesicles in the endothelial cells. Acute changes in glycemia induced structural changes in the ME which would maximize the transfer of glucose to regions of the hypothalamus involved in glucosensing.

Disclosures: F.A. Martinez Acuña: None. **M. Cifuentes:** None. **K. Salazar:** None. **N. Jara:** None. **F. Nualart:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

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Program#/Poster#: 616.20/V10

Topic: E.07. Food Intake and Energy Balance

Support: NIH Grant GM109817

Title: Identification and provisional mapping of a novel population of hypothalamic calbindin-immunoreactive neurons that project to the hypothalamic paraventricular nucleus: A combined immunohistochemical and tract tracing study in the adult male rat

Authors: *B. DE HARO[1], A. M. KHAN[2];
[2]Biol. Sci. and UTEP Systems Neurosci. Lab., [1]Univ. of Texas at El Paso, El Paso, TX

Abstract: Calbindin (CaBn), the calcium-binding protein that is widely expressed in the mammalian central nervous system, is an important neuronal macromolecule. In the hypothalamus, the expression of CaBn has been causally linked to changes in the firing patterns of peptidergic neurons. We have shown that CaBn is widely expressed in many hypothalamic regions, and is often co-expressed with neurons expressing hypocretin/orexin (H/O), and to a lesser extent, melanin-concentrating hormone (MCH). However, the connections CaBn+ neurons make with other neurons has not, to our knowledge, ever been investigated in the hypothalamus. Here, we undertook a tract tracing study where we targeted either the retrograde tracers Fluorogold (FG), or cholera toxin subunit B (CTb) into the paraventricular hypothalamus (PVH), and analyzed the ensuing patterns of retrograde labeling of neurons within the hypothalamus. In particular, we performed multi-fluorescence immunohistochemistry and confocal/wide-field imaging to identify whether tracer-filled cell bodies expressed CaBn, H/O, or MCH; or a combination of these markers. We then mapped the distribution of these neuronal populations to the Swanson rat brain atlas (Brain Maps: Structure of the Rat Brain, 3rd edition, 2004). We found retrogradely filled neurons throughout the hypothalamus, primarily on the side ipsilateral to the injection site. Our initial mapping of these neurons (Levels 28-31 of the Swanson atlas) indicates that the hypothalamic regions containing retrogradely labeled neurons included the dorsomedial, ventromedial, and arcuate nuclei; the LHA, and the posterior hypothalamus. In the LHA, the majority of these cells were in the suprafornical, juxtadorsomedial, and the juxtaventromedial (dorsal and ventral zones) sub-regions. Whereas only some (1-10) of the retrogradely filled cells were H/O+ or MCH+, many more (30-50 neurons per case) co-expressed CaBn; of these, a small percentage (8-10 neurons) were also H/O+. Our data identify and provisionally localize a novel CaBn+ population of neurons projecting to the PVH that is widely distributed within various regions of the tuberal and posterior hypothalamus. Projections from these areas might be involved in the modulation of ingestive, neuroendocrine, and pre-autonomic functions. Based on previous work demonstrating a role for CaBn in modulating peptidergic neuronal firing rates, our data suggest the possibility that these CaBn-expressing neurons exhibit unique firing patterns as compared to their surrounding non-CaBn+ neighbors, and that CaBn may confer unique functional properties to these neurons to help influence PVH function.

Disclosures: **B. De Haro:** None. **A.M. Khan:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

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Topic: E.07. Food Intake and Energy Balance

Support: NSF Grant IOS-1121866

2CI Fellowship Center for Obesity Reversal Georgia State University

Title: Pharmacological inhibition of ventral hippocampal NMDA receptors accelerates meal onset and increases meal frequency

Authors: *R. C. HANNAPEL, M. B. PARENT;
Neurosci. Inst., Atlanta, GA

Abstract: Decades of research suggest that different mechanisms regulate meal initiation versus termination. There is extremely limited evidence regarding the mechanisms that regulate meal onset and the interval between two meals (i.e., the postprandial intermeal interval; ppIMI). We previously demonstrated that temporary inactivation of ventral hippocampal neurons at the end of a sucrose meal (i.e., during the ppIMI) accelerates the onset of the next sucrose meal, and increases meal frequency and total intake. Additionally, sucrose consumption elevates ventral hippocampal expression of the immediate-early gene activity regulated cytoskeletal-associated protein (Arc), a marker of synaptic plasticity. Collectively, these findings led us to hypothesize that ventral hippocampal neurons inhibit meal onset, and that they do so through plasticity-dependent mechanisms. As an initial test, we determined the effects of pharmacologically inhibiting ventral hippocampal N-methyl-D-aspartate receptors (NMDARs) on sucrose intake. Adult male Sprague-Dawley rats (n = 8) were implanted with a unilateral cannula aimed at either the left or right ventral hippocampus (hemisphere counterbalanced) and then trained to consume a 32% sucrose solution at a scheduled time daily. On experimental days, the rats were given the competitive NMDAR antagonist 2-Amino-5-phosphonovalerianacid (APV; 30 mM, 1 μl in phosphate-buffered saline) or vehicle (within subject design) and then given the sucrose solution. Sucrose consumption, the time between sucrose meals, and the number of sucrose meals were measured for 4 hr following the infusion. The results demonstrated that ventral hippocampal infusions of APV significantly decreased the interval between the first two sucrose meals ($p < 0.05$), increased the total number of meals consumed ($p < 0.05$), and tended to increase total intake ($p = 0.07$). These findings are consistent with the hypothesis that ventral hippocampal neurons inhibit meal onset and energy intake, and that this effect requires NMDAR-dependent synaptic plasticity.

Disclosures: R.C. Hannapel: None. **M.B. Parent:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 616.22/V12

Topic: E.07. Food Intake and Energy Balance

Support: DFG TRR 134/1, C03

Title: Effects of intranasal insulin on prefrontal-hypothalamic brain circuits in lean, fasted subjects

Authors: *L. TIEDEMANN, J. HETTEL, K. GIESEN, S. BRASSEN;
Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany

Abstract: Introduction: The homeostatic feeding-system predominantly comprises the hypothalamus and the brainstem, in which hormonal regulators of hunger and satiety trigger food intake. While animal research identified various hypothalamic sub-nuclei involved in eating behavior (Gao and Horvath, 2007), only few imaging studies in humans were able to specifically track hypothalamus engagement (Kullmann 2014). We use intranasal insulin administration combined with high resolution functional imaging to investigate how central insulin modulates homeostatic but also hedonic neural responses to food stimuli. Method: In our ongoing study, so far 10 young, healthy participants (6 women, 26.4 +/- 3.7 years) underwent a double-blind, placebo-controlled cross-over design. On two scanning days, separated by one week, after an overnight fast, participants received either intranasal insulin (160IU) or placebo (NaCl) and then performed a rating task on high and low palatable food stimuli inside the scanner (3 T, EPI multiband, 1.5mm³). Results: Imaging data analysis of the placebo session reveals that our paradigm robustly activates brain regions of the homeostatic and reward related system including the hypothalamus, ventral striatum and the ventromedial prefrontal cortex (vmPFC). Comparing insulin with placebo, activation in the medial hypothalamus and the vmPFC was significantly ($p < 0.05$ FWE) reduced in the insulin condition. Discussion: Even in this rather small sample from our ongoing study we could demonstrate that central insulin modulates intrinsic brain activation in rewarding and homeostatic brain circuits. In the context of existing findings on neural correlates of ingestive behavior, our results therefore support the assumption that effects of central insulin on the hedonic brain system together with its impact on hypothalamic and metabolic mechanisms cause reduced food intake. Functional connectivity analyses in the final sample will help us to further elucidate direct interactions between both systems as a function of central insulin activity.

Disclosures: **L. Tiedemann:** None. **J. Hettel:** None. **K. Giesen:** None. **S. Brassen:** None.

Poster

616. Food Intake and Energy Balance: Anatomy and Development

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Topic: E.07. Food Intake and Energy Balance

Support: NIH Grant R01DK071738

NIH Grant R03DA020802

Title: Ventral striatopallidal control of macronutrient intake

Authors: *D. WIRTSHAFTER, I. R. COVELO, N. HORODENSKA, J. A. LUVIANO, Z. I. PATEL, T. R. STRATFORD;
Psychology, Univ. Illinois At Chicago, Chicago, IL

Abstract: Injections of the GABA antagonist bicuculline (BIC) into the ventral pallidum (VP) induce massive increases in food intake which, in animals adapted to a diet containing separate sources of macronutrients, are preferentially directed towards fats. We attempt here to clarify the behavioral nature of this effect and its anatomical and pharmacological substrates. We conducted several experiments to characterize the factors responsible for the preferential fat intake: (1) Intra-VP BIC produces massive and selective increases in lard intake even in animals not preexposed to the individual macronutrient components. In contrast, food deprivation (DEP) in these conditions preferentially increases carbohydrate (CARB) intake. These finding suggest that the BIC effect does not depend on learning about the postingestive consequences of fat intake. (2) BIC in the VP selectively increases corn oil intake in animals adapted to a diet consisting of oil, CARB and protein. In contrast, DEP has less of an effect on oil than on CARB or fat intake. This result demonstrates the BIC preferences extend to liquid plant, as well as solid animal, fats, even though a different response is required to ingest them. (3) Intra-VP BIC selectively increases lard intake in animals given a choice between lard and a 5% sucrose solution. In contrast, DEP has a larger effect on sucrose. This result indicates that the preferential fat intake seen in the earlier experiments cannot result from difficulties in consuming the powdered CARB or protein dietary components. (4) In animals adapted to a diet consisting of powdered protein and of equicaloric gelatins containing high concentrations of either lard or CARBs, BIC in the VP increased the intake of both gelatins with no effect on protein intake. This result suggests that animals are not detecting fat per se, but rather prefer the “mouth feel” typical of fats. In contrast, DEP increased intake of protein and of CARB-gelatin more than lard-gelatin, again emphasizing that BIC and DEP induce different patterns of intake. In order to determine whether all orexigenic treatments of the VP induce fat selective feeding, we studied the effects of the opioid agonist DAMGO injected in the central VP. These injections significantly increased food intake, but the fat selectivity seen with BIC was not present. We also conducted similar experiments

with DAMGO in the nucleus accumbens core; we found that these injections increased feeding but, in contrast to the results of previous workers, this effect was not fat selective. The reasons for these discrepancies are not clear, but the results serve to highlight the unique effects produced by blocking GABA in the VP.

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Poster

616. Food Intake and Energy Balance: Anatomy and Development

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: E.07. Food Intake and Energy Balance

Support: NIH grant 1R21EB012707

Title: Aromatase levels in amygdala, obesity and self control: PET and personality studies

Authors: *A. BIEGON[1], N. ALIA-KLEIN[2], T. HILDEBRANDT[2], D. PARETO[3], S. KIM[4], J. LOGAN[5], J. FOWLER[6], G.-J. WANG[4];
[1]Neurol., Stony Brook Univ., Stony Brook, NY; [2]Mount Sinai Sch. of Med., New York, NY; [3]Hosp. Val d'Hebron, Barcelona, Spain; [4]NIAAA, Bethesda, MD; [5]NYU Med. Sch., New York, NY; [6]Brookhaven Natl. Lab., Upton, NY

Abstract: Aromatase is the last and obligatory enzyme catalyzing the biosynthesis of estrogens throughout the body. We hypothesized that aromatase levels in amygdala, measured by positron emission tomography (PET) and the tracer [11C]vorozole would predict body mass index (BMI), because of the amygdala's specific role in feeding related memory, food preference, ability to override hypothalamic signaled satiety, and sensitivity to estrogens. Forty three healthy men (n = 19) and women (n = 24) were recruited from the community and underwent a brain PET scan with [11C]vorozole. A subgroup of 29 subjects (17 women, 12 men) were also administered the Multidimensional Personality Questionnaire (MPQ). Another small group (N=8, men only) had body fat measurement performed in addition to BMI and PET. The total volume of distribution VTg , was derived from a graphical analysis (Logan plot) of the time activity data. Subjects were divided into 3 BMI groups, normal weight (BMI<25) Overweight(25<BMI <30) and obese (BMI>30); matched for age and sex composition. Two way ANOVA by weight class and sex revealed a highly significant effect of BMI (p=0.0008), no main effect of sex and no sex X BMI interaction, with the highest values of VTg in the normal weight group and lowest values in the

obese group. A significant negative correlation between body fat and VTg was seen in the men who had this measurement performed. Aromatase availability in the subgroup administered the MPQ exhibited a significant positive correlation with the personality trait, Constraint ($R=0.49$, $p<0.01$, Pearson correlation). These results support a role for estrogen locally produced in the amygdala in the well know effects of estrogen on appetite suppression.

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Poster

616. Food Intake and Energy Balance: Anatomy and Development

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 616.25/V15

Topic: E.07. Food Intake and Energy Balance

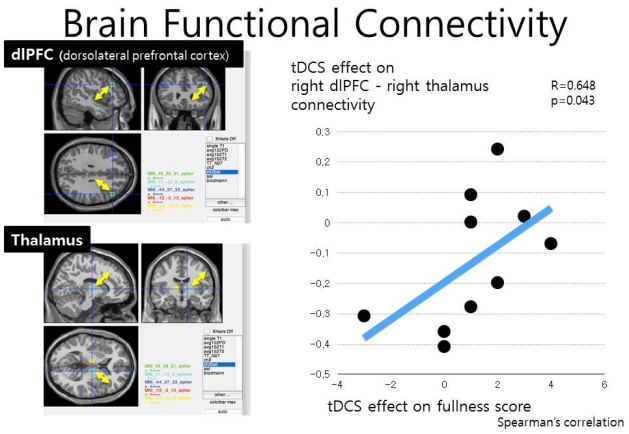
Title: Subcortical connectivity modulates effects of transcranial direct current stimulation on eating behavior in response to food cues among obese subjects

Authors: ***J.-C. KIM**[1], J. NOH[3], H. PHO[4], J. KIM[5], K. YUN[6], H. JEON[5], T. OH[5], H.-M. BAEK[3], H. CHOI[2];
[1]Med. Sci., [2]Anat., Seoul Natl. Univ., Seoul, Korea, Republic of; [3]Korea Basic Sci. Inst., Ochang, Korea, Republic of; [4]Col. of Med., [5]Chungbuk Natl. Univ., Cheongju, Korea, Republic of; [6]Caltech, Pasadena, CA

Abstract: Objective Neuroimaging studies suggest that modifying connectivity of brain circuits involved in eating behavior could provide therapeutic benefits in obesity. Transcranial direct current stimulation (tDCS) is an emerging tool for brain modulation for various diseases. We aimed to assess whether tDCS, modifies brain connectivity and behavioral response in obese subjects. Methods Fifteen overweight subjects were treated with real tDCS or sham tDCS in a cross-over design. Functional MRI (fMRI) was performed with visual food cues with high or low calorie food pictures immediately after tDCS. Questionnaires were performed to assess appetite, desire for food, mood and food addictive patterns (Yale Food Addiction Scale). Body composition and blood tests were performed. Brain connectivity was analyzed using SPM software. Results Active tDCS treatment significantly increased baseline adjusted fullness score compared with sham tDCS treatment (1.18 ± 0.98 vs. -0.18 ± 1.66, $p<0.05$) and competent mood (4.80 ± 1.14 vs. 5.60 ± 1.08, plow calorie), right precentral gyrus (high calorie<low calorie) were differently activated by visual food cues ($p<0.0001$, $k=21.3$). Active tDCS treatment significantly decreased brain activation of hippocampus, insula, pallidum, precuneus, and

orbitofrontal cortex regions (p<0.0001, k=16.1). Effect of tDCS on behavior scores were correlated with body composition and food addictive patterns (p<0.05). Effect of tDCS on fullness score was positively correlated with effect of tDCS on connectivity between right dorsolateral prefrontal cortex and right thalamus (p=0.045, r=0.648) Conclusion Brain stimulation with tDCS modulated eating behavior and subcortical brain activities. Our study implies that the brain stimulation with tDCS represents a promising option for treating obesity in humans by modulation of neural connectivity associated with reward and motivation in response to food cues.

Results



Disclosures: **J. Kim:** None. **J. Noh:** None. **H. Pho:** None. **J. Kim:** None. **K. Yun:** None. **H. Jeon:** None. **T. Oh:** None. **H. Baek:** None. **H. Choi:** None.

Poster

617. Blood Flow Functional Imaging

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 617.01/V16

Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Title: Quantitative metabolic changes and G protein-coupled receptor activation using autoradiography

Authors: O. ALITALO[1], J. RYTKÖNEN[1], T. PARKKARI[1], *T. D. WOLINSKY[2], A. NURMI[1], T. HUHTALA[1];
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Abstract: Tissue metabolism is often studied using the radiolabeled glucose analog, 2-deoxy-D-glucose (3H-2-DG), which is taken up by high-glucose-using cells in brain, kidney, and tumors. After glucose is absorbed into a cell, phosphorylation prevents it from being released; therefore metabolic activity in different brain regions can be quantified *ex vivo* through the use of autoradiography. Phencyclidine (PCP) is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that is commonly used to induce schizophrenic-like symptoms in preclinical studies. In schizophrenic patients and PCP treated rodents hypometabolism is seen in prefrontal cortex, thalamus and temporal lobes. Currently Clozapine is used in the treatment of schizophrenia. It is an atypical antipsychotic medication and it prevents impaired NMDA receptor expression caused by corresponding antagonists. The objective of the current study was to quantify metabolic changes in prefrontal cortex, thalamus and temporal lobes after PCP treatment and to determine whether pre-dosing with clozapine blocks the effect of PCP treatment. G protein–coupled receptors (GPCRs) are involved in a wide variety of physiological processes, like sight, taste, smell, behavioral and mood regulation. They activate intercellular signal transduction pathways and, ultimately, cellular responses. Ligand binding to GPCRs induces an interaction of the receptor with G protein stimulating the release of GDP simultaneously with the exchange of GTP. The use of 35S-GTPγS with autoradiography has been applied to study intracellular activation after ligand binding to GPCRs. It is possible to study activation of several different receptors at once using single radiolabeled compound since receptor activation is quantified. ARG provides universal tool to study metabolic changes and GPCR activation of novel compounds in brain. These methodologies are easily applicable to various disease models. Combining these assays with behavioral readouts provides for a rich evaluation of the pathophysiology of CNS disorders and of the mechanisms of action of novel treatments designed to treat those disorders. The current data demonstrate how the combination of assays can be utilized to advance our understanding of disease states and treatment options.

Disclosures: O. Alitalo: None. **J. Rytkönen:** None. **T. Parkkari:** None. **T.D. Wolinsky:** None. **A. Nurmi:** None. **T. Huhtala:** None.

Poster

617. Blood Flow Functional Imaging

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Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

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Title: Pharmacological blockade of inhibitory neuronal activation reduces the evoked fMRI response to LOT stimulation in the rat olfactory bulb

Authors: *A. J. POPLAWSKY[1], H. FUKUDA[1], S.-G. KIM[2];
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Abstract: Introduction: Functional magnetic resonance imaging (fMRI) measures the hemodynamic response to neuronal activity; but more evidence is needed to understand whether the evoked activity of inhibitory neurons is involved in neurovascular coupling. The olfactory bulb is an ideal model system to study this issue because inhibitory neurons are almost exclusively targeted by stimulation of the lateral olfactory tract (LOT) at synapses localized to the external plexiform layer (EPL). During stimulation, antidromic action potentials cause pre-synaptic glutamate release from dendro-dendritic synapses of excitatory mitral cells that then activate inhibitory granule cells via post-synaptic glutamate receptors. We previously showed that the fMRI signal increases due to LOT stimulation are highly localized to the evoked synapses in EPL; but it is unknown whether this vascular response is initiated by the pre-synaptic glutamate release or by post-synaptic events originating from the inhibitory neurons. Methods: In isoflurane-anesthetized rats, LOT was continuously stimulated in a block design experiment (-200 μA, 200 μs pulse duration, 40 Hz, 1 min stimulus duration, 4 min interstimulus interval); and high-resolution (110 x 110 x 500 μm3) cerebral blood volume-weighted fMRI responses were measured at 9.4 T. This contrast-enhanced fMRI technique was shown to increase sensitivity in capillaries near the site of neuronal activity. Next, to decrease the evoked activity of inhibitory neurons without affecting glutamate release, 25 mM APV (NMDA receptor antagonist) was applied to the dorsal surface of the bulb in the following paradigm: 60 min pre-drug vehicle infusion (baseline), 90 min APV infusion (drug), and 180 min vehicle washout (recovery) periods. Results: Percent fMRI signal change maps were calculated for each single LOT stimulation trial, and then trials across time were correlated to the drug delivery paradigm. Significant drug effects ($p < 0.01$ in single rats) were confined to the dorsal bulb and penetrated ~1 mm below the surface. Here, the average evoked signal change was 7.0 ± 1.8% (mean ± SEM, n = 2 rats) for the baseline, 3.2 ± 0.7% for the drug, and 5.3 ± 1.0% for the recovery periods. In control regions ventral to the drug penetration limits, the percent changes for the same three periods were 5.2 ± 1.3%, 4.8 ± 1.0%, and 4.7 ± 0.7%, respectively. Thus, the fMRI signal decreased by 53.9 ± 1.6% ($p = 0.02$, one-sample T-test) at the drug penetration site when only a 6.5 ± 3.8% ($p = 0.34$) decrease was observed in control regions. Conclusions: Our

preliminary results indicate that post-synaptic activities of inhibitory granule cells contribute to the evoked fMRI response.

Disclosures: **A.J. Poplawsky:** None. **H. Fukuda:** None. **S. Kim:** None.

Poster

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UNC School of Medicine

UNC Department of Psychiatry

Human Frontier Science Program: A control systems approach to understanding brain and behavior

UNC Startup Fund

Title: Resting state fmri of the ferret: sensory, default mode, and higher-order networks

Authors: ***Z. C. ZHOU**[1], A. P. SALZWEDEL[2,3], S. RADTKE-SCHULLER[1], Y. LI[1], K. K. SELLERS[1,4], Y.-Y. I. SHIH[5,3,6], F. FRÖHLICH[1,4,7,8], W. GAO[2,3];
[1]Psychiatry, [2]Dept. of Radiology, [3]Biomed. Res. Imaging Ctr., [4]Neurobio. Curriculum, [5]Neurol., [6]Biomed. Engin., [7]Cell Biol. and Physiol., [8]Neurosci. Ctr., Univ. of North Carolina - Chapel Hill, Chapel Hill, NC

Abstract: Translational research benefits from a diverse set of animal model species for the study of physiological and pathological brain networks. In particular, resting state functional connectivity has emerged as a powerful tool for the assessment of large-scale brain connectivity. However, no such examination of functional connectivity has been performed in ferrets, an intermediate model species that has recently gained traction for the study of higher-order brain function. Here, we present evidence for distinct networks in the ferret brain that exhibit similar topology and connectivity patterns to those observed in humans. We performed independent component analysis (ICA) and seed-based connectivity analysis on resting state function magnetic resonance imaging (fMRI) data collected from anesthetized female ferrets (*Mustela*

putoris furo). A 10 minute resting state echo-planar imaging scan was performed for each animal using a Bruker 9.4T scanner. Animals were anesthetized with 0.5-1% isoflurane and xylazine and paralyzed with vecuronium bromide. Group analysis from four animals reveal three distinct functionally connected sensory networks (visual, auditory, and somatosensory), and three "higher-order" networks ($p < 0.05$, 20 voxel minimum). Among these higher-order networks, we identified a putative default mode network (DMN) composed of the medial frontal cortex, anterior and posterior cingulate cortex, lateral temporal (auditory) cortex, lateral posterior parietal cortex, prelimbic cortex, and premotor cortex. This network shows similar topology to the DMN in humans and macaques (1). The second network was composed of the orbitofrontal cortex, dorsal lateral frontal cortex, posterior cingulate cortex, insula cortex, and premotor cortex. The third higher-order visual network consisted of extrastriate cortex and posterior parietal cortex. Seed-based connectivity maps showed connectivity patterns consistent with the results from the ICA approach ($p < 0.05$, 20 voxel minimum). These results suggest the presence of distributed, functionally connected networks in the ferret brain. The similarity in the organization of these functional networks to those in the human brain further supports an expanded role of the ferret in basic and translational neuroscience. Gaps in the characterization of the ferret brain limit our ability to draw conclusive similarities between ferret and human brain networks; however, this study highlights the importance of further delineating subdivisions of the ferret brain using both structural and functional methods. (1) Vincent JL, Patel GH, et al. Nature. 2007 May 3

Disclosures: Z.C. Zhou: None. **A.P. Salzwedel:** None. **S. Radtke-Schuller:** None. **Y. Li:** None. **K.K. Sellers:** None. **Y.I. Shih:** None. **F. Fröhlich:** None. **W. Gao:** None.

Poster

617. Blood Flow Functional Imaging

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Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Title: Neurovascular coupling in motor cortex: Inversion of the hemodynamic response as a property of baseline cortical state

Authors: *R. E. SLACK, P. PATEL, L. BOORMAN, M. JONES, J. BERWICK; Psychology, Univ. of Sheffield, Sheffield, United Kingdom

Abstract: Alterations in cortical state as shown by electrophysiological recordings of neural activity are thought to be heavily involved in priming for sensory discrimination (Zagha et al.,

2013). A corollary of these cognitive benefits is that state changes have also been shown to have critical effects on global cerebral perfusion (Braun et al., 1997). However at a detailed level, we still know little about how changes in state may impact the interpretation of well used imaging techniques such as Blood Oxygen Level Dependent (BOLD) functional magnetic resonance imaging (fMRI) which measure a cerebral vascular response, rather than actual changes in neural activity. We used an anesthetised rodent model to record neural signals from two 16 channel electrodes inserted in the whisker somatosensory and motor cortex respectively. At the same time, we recorded the vascular response using 2D Optical Imaging Spectroscopy (2D-OIS) to investigate the impact of cortical state changes on the concomitant hemodynamics. Our investigation indicates that the cortical state is key for the interpretation of spontaneous and evoked hemodynamic responses. The hemodynamic response to a 16s 5Hz electrical stimulation of the whisker pad showed a significant difference in somatosensory cortex dependent upon the pre-stimulus neural baseline state. Additionally during these same state changes, we found that the hemodynamic response in motor cortex switched from an increase to a decrease in total haemoglobin concentration (Hbt), and that the inversion of the response was dependent upon the pre-stimulus neural baseline state. These state dependent hemodynamic changes have important implications for vascular based brain imaging tools such as BOLD fMRI, especially when used in isolation. If brain state can cause the same stimulus in the same region, in this case motor cortex, to respond with an inverted hemodynamic response, this could cause a serious confound in the interpretation of fMRI signals and strongly suggests the assessment and categorisation of baseline brain state is necessary for greater information gain, particularly in the analysis of single trial datasets. An understanding of the neural signals controlling the hemodynamic response in whisker motor cortex may be generalizable to other brain regions and may be important for the understanding of fMRI signals, specifically the negative BOLD signal.

Disclosures: R.E. Slack: None. **P. Patel:** None. **L. Boorman:** None. **M. Jones:** None. **J. Berwick:** None.

Poster

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R01 NS063226 (NINDS)

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Human Frontier Science Program (HFSP)

NSF 0954796

Title: The effects of endothelial dysfunction on neural activity, hemodynamics and neurovascular coupling

Authors: *M. A. SHAIK[1], S. H. KIM[2], Y. MA[2], T. H. ZHAO[2], E. M. C. HILLMAN[2]; [2]Biomed. Engin., [1]Columbia Univ., New York, NY

Abstract: Accumulating evidence suggests that the vascular endothelium plays an integral role in driving functional hyperemia in response to neural activity in the brain. In a recent study, we demonstrated that specific and localized disruption of endothelial signaling in the vasculature via ROS-mediated damage abruptly interrupts the propagation of vasodilation in the pial arterioles, altering the overall hemodynamic response to stimulus. We have also previously observed apparent high-speed propagation of vasodilation along pial arterioles suggesting the involvement of established fast endothelial signaling mechanisms, which are known to be altered during endothelial dysfunction. Recognizing that there are many systemic physiological conditions that directly affect endothelial health, including cardiovascular disease, hypertension and diabetes, we therefore hypothesize that these diseases states could lead to altered neurovascular coupling in the brain. Furthermore, in conditions where functional hyperemia is not fully responsive to neural activity, such impaired neurovascular coupling could lead to acute neural deficits and long-term neurodegeneration. To study the interplay between endothelial health and neurovascular coupling, we have developed a wide-field optical imaging system capable of recording neural activity (via Thy1-GCaMP), oxygenation dynamics and speckle-based blood flow in awake, behaving mice. We use a newly developed mathematical model to predict hemodynamic activity from neuronal recordings. The optimally fitted hemodynamic response function (HRF) is compared between mice with healthy and disrupted endothelial signaling. Endothelial dysfunction is introduced via BBB impermeable pharmacological manipulation or with mouse models of systemic vascular disease. Changes in both neuronal activity and the HRF are compared under stimulus and resting state paradigms across a large area of the cerebral cortex. These results should provide new insights into the role of systemic vascular dysfunction in neuronal dysfunction with the overall goal of identifying therapeutic opportunities for conditions with a neurovascular component.

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Poster

617. Blood Flow Functional Imaging

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Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Title: Blood oxygenation level dependent (BOLD) contrast based pharmacological MRI in naïve rats and mice

Authors: *K. LEHTIMÄKI[1], A. NURMI[1], O. KONTKANEN[1], P. J. SWEENEY[1], L. PARK[2]; [1]Charles River Discovery Res. Services Finland, Kuopio, Finland; [2]CHDI Management/CHDI Fndn., Los Angeles, CA

Abstract: Pharmacological MRI (phMRI) is an innovative technique that allows researchers to non-invasively map brain function in response to the hemodynamic changes induced by the introduction of pharmacological stimuli. Blood oxygenation level dependent (BOLD) contrast is one of three main approaches that can be employed in order to obtain a spatial and temporal distribution as well as strength of the activation upon pharmacological stimulus in the brain (the others being: relative cerebral blood volume (rCBV) using iron oxide based contrast agents for gauging cerebral blood volume and arterial spin labeling for cerebral blood perfusion (ASL)). BOLD functional MRI represents the most promising translational tool between pre-clinical and clinical research because it is a widely accepted method in clinical functional brain studies. In this pre-clinical proof-of-concept framework, we have established BOLD phMRI measurements in 7T and 11.7T MR field strengths in anesthetized naïve rats and mice. Validation work has been carried out on the use of several different anesthetic agents both with, and without, mechanical ventilation. It is shown here that paralyzed and ventilated animals under urethane anesthesia maintain the most optimal physiological status under testing conditions and give the most reliable detection of brain responses upon introduction of pharmacological stimuli. Time series data for the BOLD phMRI were acquired using a single-shot spin-echo EPI sequence both in rats and mice and at both field strengths (7T and 11.7T). Time-resolution of functional images was 2 seconds and the functional paradigm consisted of a 20 minute scanning period pre-dosing followed by the bolus injection of the pharmacological agent to be studied (here shown as nicotine and amphetamine responses) and a 40 minute follow-up period. Physiological parameters (temperature, ECG) and pre and post scan arterial blood gases were recorded in order to confirm a consistent physiological status of the animals during the scans. Data were pre-processed with slice-timing and motion correction and spatial smoothing before registration to a reference brain for group-analysis. Results are shown as group-level independent component analysis maps and region of interests (ROI) based time- and dose-response curves. The results and the technical framework established within this study, provide a means to approach drug testing in various pre-clinical rat and mouse models in order to obtain a temporal and spatial profile of the studied compounds at different concentrations and routes of administration.

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Poster

617. Blood Flow Functional Imaging

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Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Title: Dissociable spatial properties of functional connectivity in gray and white matter

Authors: ***M. J. TOBIA**, D. GALLAGHER, R. DEWAL, P. KARUNANAYAKA, Q. YANG; Dept. of Radiology, Hershey Med. Ctr., Hershey, PA

Abstract: Resting state fMRI (R-fMRI) has uncovered the large-scale network organization of the human brain via functional connectivity analyses, which has greatly enriched systems neuroscience. R-fMRI functional connectivity is based on correlations of low frequency fluctuations (LFFs) between neighboring and/or long distance voxels. In general, functional connectivity in gray matter (GM) is attributed to the blood oxygenation level dependent (BOLD) effect, and voxels in white matter (WM) are uncorrelated to GM due to lack of BOLD. However, WM voxels also display LFFs and significant correlations among themselves, suggesting a non-BOLD mechanism of functional connectivity in WM. In addition, the WM contains electric current propagating along fiber tracts. We, thus, hypothesize that the correlation of LFFs in WM is caused by its electric current, and WM functional connectivity would be anisotropic and oriented along its fiber tracts. To test our hypothesis, we analyzed R-fMRI data using a local functional connectivity (LFC) tensor to quantify the anisotropy of correlated LFFs in WM. Computation of the LFC tensor involves two steps: 1) compute the Pearson correlation between a home voxel and each voxel in its 3D neighborhood defined as a radius of 2 voxels, and 2) fit the tensor model to the local correlation matrix using linear least squares. This process is repeated to generate a tensor for every voxel, from which metrics for the average spatial correlation (ASC) and anisotropy can be derived. R-fMRI data were collected from 12 healthy young adults with eyes closed (TR = 2 sec; 150 volumes). After standard preprocessing, nuisance regression and bandpass filtering (.008-.1 Hz), the LFC tensor was computed for each voxel. We expected the ASC to be greater in GM than WM due to the BOLD effect in GM only, and we expected the anisotropy to be greater in WM due to electric currents along anisotropic fiber tracts. The group average ASC was greater in GM (.45, +/- .05) than WM (.33, +/- .03). A two-sample t-test revealed a highly significant difference between GM and WM, $t(22) = 8.56$, $p = 1.8e-08$. The

group average anisotropy was greater in WM (.26, +/- .07) than in GM (.24, +/- .07), t(22) = -2.28, p = .03. These different spatial properties of functional connectivity show that the mechanism of correlation among voxels is different between GM and WM, and suggests that WM R-fMRI is influenced by oscillating electric signals that propagate along anisotropic fibers in the brain.

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Poster

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Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

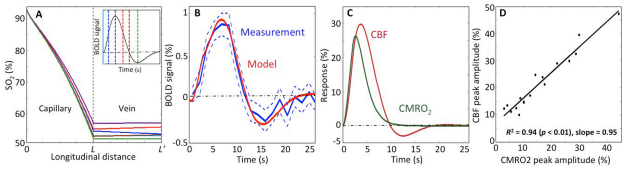
Support: NIH grant R21HL108143

Title: Novel BOLD model for hemodynamic response with brief stimulation in the human brain

Authors: *J. KIM, D. RESS;
Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Most attempts to explain the BOLD response have assumed non-linear venous dilation, thus yielding “balloon” models. However, recent brief stimulation experiments showed prompt arterial dilation without venous volume changes. Accordingly, we assume that arterial dilation creates an underdamped flow (CBF) response to yield a new “arterial impulse” model. The CBF and oxygen demand (CMRO2) responses are combined to predict longitudinal oxygen saturation (SO2) in capillary and venous compartments, which are then linked to the BOLD signal. Our model is validated against measurements of the BOLD hemodynamic response function (HRF) evoked by brief stimulation in human visual cortex. Methods: The BOLD signal depends on SO2 changes in capillaries and veins. We assume a uniform cylindrical geometry for the vessels and finely grid their lengths. Model includes flow, oxygen dissociation, and diffusion into extravascular tissue, to obtain continuous SO2 spatial profiles. CBF response is modeled by a linear network, which describes the impulse response produced by prompt arterial dilation. CMRO2 response is modeled by a gamma function. The HRF was measured using a 2-s stimulus of 4-Hz flickering dots followed by a 26-s blank period. High-resolution fMRI data (0.9-mm voxels) was obtained in 7 subjects (spiral acquisition, 1.5-s/volume). Each session produced ~85 HRF responses that were averaged across visual areas V1-3. The model was fit to the HRFs by

adjusting CBF and CMRO2 parameters. Results: The model predicts substantial SO2 variations along the length of capillaries and veins (Fig A). HRF measurements are in good agreement with model fits (Fig B), which are based on estimates of the corresponding CBF and CMRO2 responses (Fig C). The model predicts an offset linear correlation with near unity slope between CBF and CMRO2 peak amplitudes (Fig D). Conclusion: We establish a new arterial impulse model based on the hypothesis that prompt arterial dilation is a key physiological mechanism for the HRF, and demonstrate its efficacy in predicting the BOLD HRF.



Disclosures: **J. Kim:** None. **D. Ress:** None.

Poster

617. Blood Flow Functional Imaging

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Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Title: Clinical and prognostic significance of brain SPECT changes in the default mode network areas

Authors: *D. G. PAVEL[1], S. R. BEST[2];
[1]PathFinder Brain SPECT, [2]The Neurosci. Ctr., Deerfield, IL

Abstract: Introduction: Resting Brain SPECT (Single Photon Emission Computed Tomography) evaluates the functional status of the gray matter. Based on the fact that it is specifically able to identify the area of the two main components of the Default Mode Network (DMN) : anterior cingulate / adjacent mesial frontal pole and, posterior cingulate / precuneus , we looked at the possible improvement of image interpretation when abnormalities in these areas were detected. Methods: In this pilot study we selected cases where marked hypo or hyperperfusions in one or both components of DMN were present and correlated them with clinical history and outcome after variable periods of followup. The brain SPECT was done with a triple head gamma camera using 99mTc_HMPAO . The display uses a discrete color code, orthogonal slices, multiple thresholded volume displays and automatic generation of 8 Talairach normalized surface views. Results 16 patients , ages 17- 69 who had a followup of 18 months or more. 6 had DMN

underperfusions (4 in the posterior and 2 in the anterior component area) and 10 had DMN hyperperfusions (3 in both components, 4 in the posterior and 3 in the anterior component). Underperfusions. The 4 patients with posterior DMN underperfusion were ultimately confirmed as Alzheimer's or mixed dementia. The 2 with anterior DMN underperfusion were in patients with significant comorbidity, one of them confirmed as early fronto-temporal lobar degeneration. Hyperperfusions. The 3 patients with hyperperfusion in both components of DMN required prolonged treatment including medication, rTMS (repetitive Transcranial Magnetic Stimulation) and/ or ketamine perfusion without or with augmentation with TMS). One 22 y.o. patient required intensive treatment over 2 ½ year involving all these protocols before transitioning from unemployable to a fully employed person with further professional goals. The remaining 8 patients with only partial DMN hyperactivity, required prolonged treatment but overall were easier to treat. Discussion We interpret these results in light of the known functional anti-correlation, normally exhibited by the DMN in the presence of conscious activity : the more extensive the abnormality, the more severe the interference is with the anti-correlation during conscious activity . This can result in prolonged system perturbations leading to the dysfunctions of comorbid mental disorders. Conclusions: The location type and amount of abnormality detected in the DMN areas can suggest the level of dysfunction present in each case, lead to better clinical understanding and also provide additional prognostic information.

Disclosures: D.G. Pavel: None. **S.R. Best:** None.

Poster

617. Blood Flow Functional Imaging

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NSF 0954796

1 F30 HL128023-01

R01 NS076628

R01 NS063226

Title: Capturing the dynamics of neuronal activity, brain oxygenation and brain blood flow during acute cortical stroke

Authors: *H. ZHAO[1], D. CHOW[2], M. G. KOZBERG[3], M. A. SHAIK[3], S. H. KIM[3], E. M. C. HILLMAN[3];
[2]Radiology, [3]Biomed. Engin., [1]Columbia Univ., New York, NY

Abstract: Determining the risks and benefits of thrombolytic therapy in stroke patients poses a major challenge. Current methods using stroke core and salvageable penumbra mismatch, a metric thought to correlate with hemorrhagic risk, have proven unreliable in clinical trials. Seeking improved metrics, we have developed a mouse model in which we can characterize the minute-by minute progression of acute stroke, with a particular focus on stroke onset. To achieve this, we use high-speed optical imaging of the bilaterally-exposed cortex of Thy1-GCaMP mice during localized, optically-induced unilateral acute stroke to simultaneously capture optical intrinsic signal, GCaMP fluorescence and laser speckle reflection data representing oxy- and deoxy-hemoglobin concentrations, neuronal activity and blood flow, respectively. We record the spatiotemporal changes of these parameters over 1-3 hours following acute stroke both with and without somatosensory stimulation. Prior to stroke, our analysis reveals bilateral spontaneous neuronal activity appearing as symmetric waves traversing the cortex. These waves become disrupted by the progression of the ischemic region during the early minutes of stroke. Prolonged ischemia attenuates these neuronal events with evidence of a gradual temporal decoupling of neuronal activity in the affected region. Our simultaneous acquisition of hemodynamic and blood flow measurements permit analysis of the order in which the neuronal and vascular deterioration occurs and can distinguish degradation of neurovascular coupling from alterations in neural network ‘functional connectivity’. Our technique provides a new approach to finding and understanding biomarkers of early stroke and therapeutic response.

Disclosures: H. Zhao: None. **D. Chow:** None. **M.G. Kozberg:** None. **M.A. Shaik:** None. **S.H. Kim:** None. **E.M.C. Hillman:** None.

Poster

617. Blood Flow Functional Imaging

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Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

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DIT Grant R&D/RDC/13(6)/2013

Title: Human MRI tensor-based corroboration of transport indices of gliovascular glymphatic fluidic system of brain for clearing Alzheimer's Amyloid

Authors: *P. K. ROY;
Natl. Brain Res. Ctr., Manesar (NCR Delhi), India

Abstract: INTRODUCTION:The clearance of amyloid and solutes from brain, via its interstitial CSF-originated Gliovascular lymphatic (Glymphatic) system has been experimentally formulated in rodent models [1]. A substantiation of this system quantitatively in the clinical human is desirable. . METHODS: . We use the Curie-Neumann principle to elucidate that the transport tensors in a fluidized phase of brain interstice share eigenvectors. We infer that in each brain voxel, there would be common eigenvectors of diffusion mobility tensor D and that of other mobility tensor (say convection tensor or fluid permeation tensor). Using 3 tesla Philips MRI scanner on human subjects, we delineate how one can construct the general transport tensor from MRI diffusion tensor for each voxel by choosing a set of basis functions in which both the tensor ellipsoids become in parallel format. Cross-property relationships are delineated by a statistical correlation expansion of the tissue's microstructure consisting of a parenchymal matrix space embedding an amorphous convoluted glymphatic space. . RESULTS: . We show the linearity between eigenvalues of tensors as that of permeation and perfusion processes, using experimental findings, from diffusion tensor imaging and fluidic mobility measurement. We find that different transport processes, when analyzed using our generalized tensor imaging approach [2], are actually interrelated due to boundary condition of tissue geometry, where the thermodynamic transport tensors related are fluidic permeation tensor, molecular diffusion tensor or haemodynamic perfusion tensor. Using the aforesaid generalized tensor MRI approach developed, we noninvasively estimate the energy flux index, diffusion index and conduction index for the interstitial fluid phase to be respectively 0.49 W/m/K, 5.62 um^2/ms and 4.85 siemens/m. These values are respectively within 94%, 85% and 94% of surgically measured values of those indices in the fluidic phase of the lymphatic system using invasive electrodes, whence the mean predictive accuracy of our mathematical model is 91%. Using thermodynamic transport principles [3], we obtain a quantitative approach to solute/amyloid clearance from brain. . CONCLUSION: . A ready MRI-based substantiation of the glymphatic fluidic system in brain is explored in human scenario, along with indicating a thermodynamic transport approach to amyloid clearance from brain. . REFERENCES: . [1] J Iliff et al, J. Neurosci. 33: 18190-99, 2013. [2] K Budhachandra et al, Ann. Biomed. Engng. 38: 3070-83, 2010 [3] R Rastogi, Introduction to non-equilibrium physical chemistry, Elsevier, Amsterdam, 2008.

Disclosures: P.K. Roy: None.

Poster

617. Blood Flow Functional Imaging

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Title: Ultra-fast MREG detection of glymphatic pulsations

Authors: *V. KIVINIEMI[1], X. WANG[2], V. KORHONEN[1], P. LEVAN[3], S. KEILHOLZ[4], M. NEDERGAARD[5];
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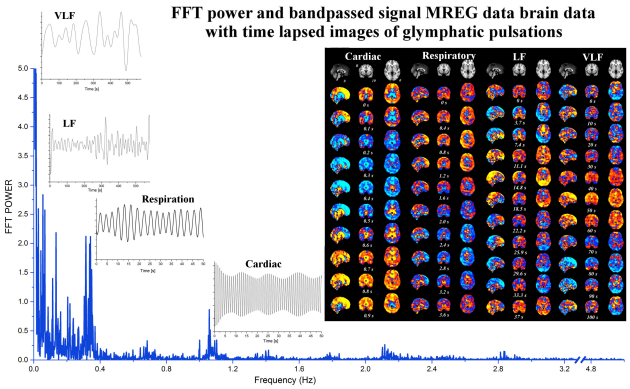
Abstract: Background: Glymphatic convection of CSF through the extra-cellular matrix is partially mediated by cardiac pulsations . We investigated if we could identify more sources for glymphatic pulsations in the human brain with ultra-fast MREG sequence. Methods: Nine subjects were scanned in rest after informed consent using 3T MREG sequence. MRI-compatible ECG was used to identify cardiac T-peak (ECG 0.8-1.2 Hz) and bellows for respiratory (0.15 - 0.35 Hz) frequencies. Low frequency (LF 0.027-0.073 Hz) and very low frequency (VLF 0.01-0.027 Hz) waves were identified from MREG data with FSL groupPICA dual-reg. QPP algorithm to separate pulsations from MREG data . Results: Three different physiological mechanisms of brain pulsations were identified; periodic cardiac and respiratory pulsations and quasiperiodic VLF/LF waves. The cardiac pulsations originated from basal peri-arterial regions extending centrifugally. Respiratory pulsations extended centripetally in cortical peri-venous areas. The VLF/LF waves had a unique quasiperiodic spatiotemporal patterns related to separate vasomotor control mechanisms. Conclusion: Critically ultra-fast MREG data opens a new view into human brain physiology by enabling comprehensive 3D imaging of glymphatic pulsations mechanisms. Basically this opens a new way to image abnormal brain pulsations early in the course of glymphatic system failures. References: 1Nedergaard, Maiken. Science 340(6140) 1529-30. 2 Majeed, et al. NeuroImage 54, 2: 1140-50.



Disclosures: **V. Kiviniemi:** None. **X. Wang:** None. **V. Korhonen:** None. **P. Levan:** None. **S. Keilholz:** None. **M. Nedergaard:** None.

Poster

617. Blood Flow Functional Imaging

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 617.13/V28

Topic: E.09. Brain Blood Flow, Metabolism, and Homeostasis

Support: NINDS Grant R01NS085200

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National Natural Science Foundation of China 81101025

Title: Genetic influences on resting-state networks: a twin study

Authors: ***Z. MA**[1], Y. FU[2], C. HAMILTON[1], Z. LIANG[1], X. HOU[4], X. MA[2], X. HU[2], Q. HE[3], W. DENG[5], Y. WANG[5], L. ZHAO[5], H. MENG[2], T. LI[5], N. ZHANG[1];
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Abstract: Abnormalities of resting-state networks (RSNs) are often associated with neuropsychiatric diseases. Given this critical correlation, it has been hypothesized that RSNs can be used as an endophenotype (Khadka, et al., 2013). A foremost step for testing this hypothesis is to examine the heritability of RSNs. However, the investigation of the genetic basis of RSNs has

been limited in the default mode network at the region-of-interest level (Korgaonkar, et al., 2014), while the genetic control on other RSNs has not been determined yet. In the present study, we examined the genetic influences on eight well-characterized RSNs using a twin design. Using the resting-state functional magnetic resonance imaging data collected from 32 monozygotic and 24 dizygotic twin pairs, RSNs were extracted using group independent component analysis (Calhoun, et al., 2001). The genetic effects on each RSN were quantified by fitting the functional connectivity covariance of each voxel in the RSN to the classic ACE twin model (Neale and Cardon, 1992). The data showed that although environmental effects accounted for the majority of variance in wide-spread areas, there were specific brain regions that showed significant genetic control for individual RSNs. In addition, there was large variability in genetic influences across different RSNs. Sensory networks tend to be under stronger genetic control relative to cognitive networks. These results suggest that part of the human brain functional connectome is shaped by genetic constraints. Importantly, this information can be useful for bridging genetic analysis and network-level assessment of neuropsychiatric diseases.

Disclosures: **Z. Ma:** None. **Y. Fu:** None. **C. Hamilton:** None. **Z. Liang:** None. **X. Hou:** None. **X. Ma:** None. **X. Hu:** None. **Q. He:** None. **W. Deng:** None. **Y. Wang:** None. **L. Zhao:** None. **H. Meng:** None. **T. Li:** None. **N. Zhang:** None.

Poster

618. Spatial Memory

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 618.01/V29

Topic: F.01. Human Cognition and Behavior

Title: Cognitive factors associated with spatial navigation

Authors: ***M. FRAHMAND**[1], L. KORTHAUER[2], N. T. NOWAK[2], I. DRISCOLL[2];
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Abstract: Although effective spatial navigation requires memory for objects and locations, other cognitive factors may also impact performance. The virtual Morris Water Task (vMWT) is a translational version of the classic paradigm used to investigate place learning and memory in rodents. The vMWT requires participants to acquire, consolidate, and retrieve distal environmental cues to navigate a large pool and find a hidden escape platform. Previous research has explored associations between vMWT performance and neuropsychological tests of visuospatial abilities or memory, but effective navigation may also require considerable

executive resources to select search strategies and monitor performance. Executive functions refer to higher-level control of cognitive processes, including cognitive flexibility, planning, and logical reasoning. The objective of this study was to assess associations between spatial navigation and cognitive abilities in three areas: 1) executive functioning (measured using Delis-Kaplan Executive Function System [D-KEFS] Towers, Category Switching, and Color-Word Interference subtests); 2) verbal skills (category and lexical fluency tasks); and 3) visuospatial ability (Mental Rotations Task). We hypothesized that higher executive functioning and visuospatial abilities, but not verbal skills, would be associated with lower latency and distance to complete vMWT learning trials. Furthermore, we predicted that associations between executive functioning and navigation performance would be strongest during the first trial of the vMWT, which requires selection and employment of effective search strategies. Participants included 55 adults (8 males, 47 females; ages 18-52). As predicted, higher total latency to complete vMWT learning trials was associated with lower set switching ($r = -.33$, $p = .03$) and longer time to complete the Color-Word Interference task ($r = .3$, $p < .05$), which measures ability to inhibit irrelevant information . Longer vMWT total distance was also associated with more errors on a visuospatial task requiring mental rotation of objects ($r = .41$, $p < .01$). Regarding performance on the first trial of the vMWT, the association between lower latency to find the hidden platform and higher set switching accuracy trended toward significance ($r = -.27$, $p = .06$). Our findings indicate that the ability to inhibit irrelevant information, use logical reasoning, and switch between mental sets are important considerations in one's ability to spatially navigate, in addition to memory and visuospatial ability. This may inform our knowledge of factors that may contribute to age-related differences in navigation performance.

Disclosures: **M. Frahmand:** None. **L. Korthauer:** None. **N.T. Nowak:** None. **I. Driscoll:** None.

Poster

618. Spatial Memory

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 618.02/V30

Topic: F.01. Human Cognition and Behavior

Support: NIA AG032361 (PI: Driscoll)

Title: Virtual water maze performance in middle-aged adults

Authors: *N. T. NOWAK[1], J. DOSHI[2], L. KORTHAUER[1], E. AWE[1], C. DAVATZIKOS[2], I. DRISCOLL[1];
[1]Psychology, UW - Milwaukee, Milwaukee, WI; [2]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Spatial navigation performance declines with age and often shows a male advantage. Computerized versions of traditional rodent learning and memory tasks, such as the virtual Morris water maze (vMWM), provide a means to test human navigation in a controlled setting. Navigation outcomes have been related to the BOLD response, identifying a number of brain regions associated with performance, including the hippocampus, caudate nucleus, parahippocampal gyrus, prefrontal, parietal, and posterior cingulate cortices. Brain structural integrity declines with age and has also been related to navigation. For example, the volumes of some of these same areas identified with fMRI were related to age differences in navigation performance (e.g., Moffat et al., 2007). The purpose of this study was to assess the relationships between age, sex, vMWM performance and volumes of brain regions implicated in navigation. Imaging was performed on a 3T GE scanner at the Medical College of Wisconsin. A multi-atlas label fusion method was applied for ROI segmentation (Doshi et al., 2013). Multiple atlases were warped individually to the target image (Ou et al., 2011). An image intensity based term was used for modulating the segmentations in the boundaries of the ROIs according to the intensity profile of the subject image. Volumetric measurements were calculated in each ROI. Our sample (N = 103; 59 women) of non-demented individuals (Dementia Rating Scale: M=140; MMSE = 29) ranged between 40 and 61 years of age (M = 51). Older age was associated with more time and longer distance to find the hidden platform, and greater heading direction error across the hidden platform and probe trials (p's ≤ 0.05). We rated each participant's strategy as either "place" (i.e., taking a relatively direct path from start to platform) or "random" (i.e., relatively circuitous path) from maps of their search paths. Those categorized as using a place strategy outperformed those categorized as using a random strategy on most measures of navigation performance (p's ≤ 0.05). In contrast to many studies of younger adults, we did not observe a male advantage in vMWM performance. We did not observe significant relationships between navigation and gray matter volumes (e.g., hippocampus, caudate nucleus) that have been reported in samples that include younger and older adults, albeit significant brain atrophy is not expected within our narrow age group of middle-aged adults. However, our results are congruent with the age-related deficit in navigation performance reported in other studies, and provide further evidence that wayfinding may begin to decline in middle age before the detection of overt cognitive impairment.

Disclosures: **N.T. Nowak:** None. **J. Doshi:** None. **L. Korthauer:** None. **E. Awe:** None. **C. Davatzikos:** None. **I. Driscoll:** None.

Poster

618. Spatial Memory

Location: Hall A

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Program#/Poster#: 618.03/V31

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant AG032361

Title: Associations between pattern separation and structural brain integrity in middle age

Authors: *L. E. KORTHAUER, N. T. NOWAK, E. AWE, I. DRISCOLL;
Univ. of Wisconsin-Milwaukee, Milwaukee, WI

Abstract: Pattern separation is a process that segregates overlapping information, reduces interference, and allows the establishment of unique representations between memories that share similar elements. Transverse patterning discrimination task (TPDT) requires pattern separation for successful performance and is dependent on the hippocampus, a structure critical for normal learning and memory and often implicated in age-related cognitive decline (Driscoll & Sutherland, 2005). The aim of the present study was to characterize TPDT performance in midlife and to identify associations with structural brain integrity, as subtle differences in brain-behavior relationships may emerge years before the onset of overt impairment. Healthy adults (n = 71) aged 40 to 60 completed the TPDT and underwent multimodal MR imaging. The TPDT begins with a set of three phases of elemental discriminations (A+B-, C+D-, E+F-; non hippocampus-dependent). Phases 4-6 are transverse patterning discriminations (phase 4: G+H-; phase 5: G+H- and H+I-; phase 6: G+H-, H+I-, I+G-). To assess structural brain integrity, cortical reconstruction and volumetric segmentation of T1-weighted SPGR data was performed with Freesurfer Version 5.3.0 (http://surfer.nmr.mgh.harvard.edu). Within this middle-aged sample, older age was associated with more trials to complete the transverse patterning phases ($p < .01$), while there was no association between age and the number of trials to acquire elemental discriminations. The associations between hippocampal volume and number of trials to acquire elemental or transverse patterning discriminations after controlling for age and intracranial volume were not significant. However, a higher number of trials to complete transverse patterning was associated with lower cortical thickness across a range of frontal brain regions, including the left frontomarginal gyrus ($p = .01$), left transverse frontopolar cortex ($p = .02$), bilateral inferior frontal cortex ($p's < .05$), bilateral middle frontal sulcus ($p = .04$), and right superior frontal sulcus ($p = .02$). Significant correlations were also found in the anterior ($p < .01$) and mid-anterior ($p = .04$) cingulate cortex and bilaterally in the pre- and post-central gyri ($p < .05$); more trials to complete transverse patterning were associated with thinner cortex in these regions. These correlations remained significant after controlling for age. Collectively, these findings suggest that age-related deficits in pattern separation may begin in middle age and that

TDPT performance is associated with the structural integrity of underlying brain regions, particularly in the frontal cortex.

Disclosures: **L.E. Korthauer:** None. **N.T. Nowak:** None. **E. Awe:** None. **I. Driscoll:** None.

Poster

618. Spatial Memory

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 618.04/V32

Topic: F.01. Human Cognition and Behavior

Support: ONR MURI Grant N00014-10-1-0936

Title: Which way and how far? Tracking of translation and rotation information for human path integration

Authors: ***E. R. CHRASTIL**[1,2], K. R. SHERRILL[1,2], M. E. HASSELMO[1], C. E. STERN[1,2]; [1]Dept. of Psychological & Brain Sci., Boston Univ., Boston, MA; [2]Athinoula A. Martinos Ctr. for Biomed. Imaging, Charlestown, MA

Abstract: Path integration, the constant updating of a navigator's knowledge of position and orientation during movement, requires both visuospatial knowledge and memory. This study aimed to resolve current questions regarding distance coding in the human brain and to additionally investigate coding of rotation signals that are also important for navigation. To achieve these goals, this study examined the brain mechanisms that support the tracking and memory of translational and rotational components of human path integration. We used functional imaging to investigate two fundamental elements of path integration: 1. Distance tracking: translation in a straight line, and 2. Angle tracking: rotation in place. Critically, movement had no defined end-point or goal, in contrast to previous studies. Rather, navigators accumulated translational and rotational information during passive virtual self-motion. Univariate parametric results show that activity in hippocampus, retrosplenial cortex (RSC), and parahippocampal cortex (PHC) increased with movement during both distance and angle encoding, suggesting these regions track translation and rotation during path integration. By implementing a modified delayed match to sample (DMS) paradigm, we also examined the encoding and maintenance of path integration signals. Results of the DMS paradigm showed that hippocampus, RSC, and PHC were recruited during successful encoding and maintenance of path integration information, with RSC selective for tasks that required processing heading angle changes. Preliminary functional connectivity analysis of this navigational network, as well as

motion processing areas hMT+ and V6 and frontal executive function regions mPFC and dlPFC, showed functional connections between these areas during both encoding and delay. These results suggest that processing in this navigational hub (hippocampus, PHC, and RSC) relies on communication with regions sensitive to optic flow (hMT+ and V6) and executive function areas (mPFC and dlPFC). Furthermore, these functional connections were stronger for participants who were more accurate at the two tasks, suggesting that coordinated processing by brain regions in multiple networks could underlie individual abilities in human path integration. Together, the results provide evidence that hippocampus, PHC, and RSC flexibly track task-relevant translation and rotation signals for path integration and could form the hub of a more distributed network supporting spatial navigation.

Disclosures: E.R. Chrastil: None. **K.R. Sherrill:** None. **M.E. Hasselmo:** None. **C.E. Stern:** None.

Poster

618. Spatial Memory

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 618.05/V33

Topic: F.01. Human Cognition and Behavior

Title: High confidence false memory for spatial context is mediated by the parahippocampal cortex

Authors: *J. M. KARANIAN, S. D. SLOTNICK;
Psychology, Boston Col., Chestnut Hill, MA

Abstract: Prior research suggests that the primary role of the parahippocampal cortex is processing of spatial layouts and sensory details (e.g., Epstein & Kanwisher, 1998; Epstein & Ward, 2010), while other work suggests that the parahippocampal cortex mediates spatial and non-spatial contextual processing (e.g., Diana et al., 2011; Eichenbaum et al., 2007). The large majority of studies have reported that parahippocampal cortex activity is greater during true memory than false memory, which seems to support the sensory processing hypothesis as true memories have greater sensory detail than false memories. However, contextual details were also greater for true memory than false memory in these studies such that sensory processing and contextual processing were confounded. To better assess the role of the parahippocampal cortex, in a previous fMRI study, we dissociated sensory and contextual processing for true memory and false memory so that false memories required relatively more contextual processing than true memories (Karanian & Slotnick, 2014). In that study, we found greater parahippocampal cortex

activity for false memory than true memory, which supports the contextual processing hypothesis. In the present fMRI study, we further investigated the role of the parahippocampal cortex by assessing activity in this region as a function of context memory confidence. We hypothesized that high versus low confidence false memories for spatial context would be associated with greater activity in the parahippocampal cortex, under the assumptions that high confidence false memories are associated with relatively greater spatial context processing and that both high and low confidence false memories lack sensory detail. Data from 16 participants were acquired at 3T with a 32-channel head coil and a random-effect general linear model analysis was conducted. During encoding, participants viewed abstract shapes to the left or right of fixation. During retrieval, old items were presented at fixation and participants identified the context of each item as either previously in the "left" or "right" visual field followed by an"unsure"-"sure"-"very sure" confidence rating. Preliminary analyses revealed greater parahippocampal cortex activity for high confidence false memories (context incorrect-"very sure") as compared to low confidence false memories (context incorrect-"unsure"). To our knowledge, this is the first time that the parahippocampal cortex has been found to be modulated as a function of context memory confidence. These findings provide additional support for the hypothesis that the parahippocampal cortex mediates contextual processing.

Disclosures: J.M. Karanian: None. **S.D. Slotnick:** None.

Poster

618. Spatial Memory

Location: Hall A

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Topic: F.01. Human Cognition and Behavior

Support: NSF GRFP

NSF IGERT 0801700

NIH 1R01EY02391501A1

NIH 1R01EY02231801A1

Title: Visual field position biases in the human medial temporal lobe

Authors: *K. F. LAROCQUE, N. WITTHOFT, K. GRILL-SPECTOR, A. D. WAGNER; Dept. of Psychology, Stanford Univ., Stanford, CA

Abstract: The medial temporal lobe (MTL) is known to play a critical role in episodic memory. Functional neuroimaging and lesion data suggest that MTL subregions play differential roles in processing distinct types of event content, with perirhinal cortex (PRc) and parahippocampal cortex (PHc) playing differential roles in processing complex visual stimuli (e.g., faces, objects) and visuospatial information (e.g., scenes), respectively. Here, we examined whether MTL subregions play differential roles in processing content that is encountered in distinct positions in the visual field. Specifically, we examined whether eccentricity biases present in visual cortical regions that differentially project to MTL subregions are propagated forward to these MTL subregions, and whether biases for stimuli presented in the contralateral visual field are also propagated forward to the MTL. In two studies (n = 6, n = 5), participants underwent fMRI at 3T. Participants maintained fixation while viewing visual stimuli presented in different locations across the visual field. MTL subregions were anatomically defined in native space for each participant. Within each subregion, we examined the degree of activation for stimuli presented in the center relative to the periphery of the visual field (eccentricity bias), and within each hemisphere of each subregion, we examined the degree of activation for stimuli presented in the contralateral relative to ipsilateral visual hemifield (hemifield bias). In both studies, PRc and PHc showed differential eccentricity biases: PRc showed a stronger bias for stimuli presented in the center of the visual field relative to PHc. Additionally, MTL subregions showed biases for stimuli presented in the contralateral visual hemifield. These findings suggest that visual field biases are present in MTL subregions, with distinct MTL subregions demonstrating distinct visual field biases, and provide insights into the roles that these subregions play in declarative memory for distinct types of event content.

Disclosures: K.F. Larocque: None. **N. Witthoft:** None. **K. Grill-Spector:** None. **A.D. Wagner:** None.

Poster

618. Spatial Memory

Location: Hall A

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Program#/Poster#: 618.07/V35

Topic: F.01. Human Cognition and Behavior

Support: DARPA Grant ARO:W911NF-14-1-0157

Title: Incongruent visual animations make unrelated narratives more memorable by driving stronger brain responses

Authors: *S. S. COHEN[1,3], L. C. PARRA[2];
[2]Biomed. Engin., [1]City Col., New York, NY; [3]Psychology, The Grad. Ctr. at the City Univ. of New York, New York, NY

Abstract: Our ability to remember a story is dependent on reliable encoding of the initial experience. We wondered if the initial encoding can be facilitated by exposing subjects to incongruent sensory stimuli via a separate sensory channel. We hypothesized that visual context, even if unrelated, will more effectively drive brain responses to an auditory narrative and therefore result in improved retrieval. To test this we presented autobiographical narratives both with and without accompanying animations while recording electroencephalographic responses and assessed memory three weeks later. We found that audiovisual narratives were recalled more effectively than the identical story presented as audio alone for all 10 stories tested. Notably, this benefit was almost as strong when the animations were incongruent with the semantics of the audio, and despite the fact that the visual information in isolation did not result in any meaningful recall. As predicted, the memory benefits coincided with an increase in the reliability of brain responses evoked by each story across individuals . Moreover, subjects with more reliable brain responses also recognized story elements better even after controlling for stimulus modality. Finally, information was retained more accurately if evoked responses were more reliable during the presentation of the relevant information. Our interpretation of these results, supported by a corresponding modulation of alpha activity, is that these audiovisual stimuli effectively engage attention, driving the brain more reliably, and making the story more memorable, even when the visuals do not contribute any factual information.

Disclosures: S.S. Cohen: None. **L.C. Parra:** None.

Poster

618. Spatial Memory

Location: Hall A

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Program#/Poster#: 618.08/V36

Topic: F.01. Human Cognition and Behavior

Support: NSERC 491728

Title: The impact of visual interference on representational content in the medial temporal lobe and ventral visual stream regions during a delayed match-to-sample task

Authors: *E. B. O'NEIL, A. C. H. LEE;
Psychology, Univ. of Toronto, Scarborough, Scarborough, ON, Canada

Abstract: Recent findings (see Graham et al. Neuropsychologia, 2010 for review) suggest that the perirhinal cortex (PRC), a medial temporal lobe (MTL) region that receives a majority of its inputs from the ventral visual pathway, supports perceptual discrimination of complex objects. This finding has led some to view PRC as the apex of the ventral visual pathway (Murray & Bussey, TICS, 1999). This role in perception is in addition to the well-known role of the MTL in declarative memory, as well as recent work pointing to a role of this region in supporting working memory for faces and objects. Despite a growing acceptance of the broader contributions of the MTL beyond declarative memory, little is known about the specialized role ventral visual stream (VSS)- and PRC-based representations serve as visual information is perceived, maintained and encoded. This is in part due to the fact that perceptual discrimination tasks typically used to probe non-mnemonic contributions of MTL structures require discriminating between several concurrently presented stimuli. Here, we used functional magnetic resonance imaging to examine MTL and VSS responses to individual stimuli in the context of a delayed match-to-sample task designed to address these issues. A study item was presented, and following a delay, participants were presented with a test item, indicating with a button press if this item differed from the study item. Critically, interfering items from a different stimulus category than the target were presented to participants while the target item was being maintained in working memory, creating conflict between the contents of working memory and ongoing perception. This design, in conjunction with representational similarity analysis and multivoxel pattern analysis approaches, allowed category evidence to be tracked and compared at each phase across the brain. Our preliminary findings revealed differential contributions of MTL and VSS structures across perception, maintenance, and interference phases. Together, our findings help shed light on the specialized nature of representations in the VSS and MTL, and how these representations support perception as well as working and long-term memory.

Disclosures: **E.B. O'Neil:** None. **A.C.H. Lee:** None.

Poster

618. Spatial Memory

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 618.09/V37

Topic: F.01. Human Cognition and Behavior

Title: Neural spatial memory ROCs indicate the hippocampus operates in a threshold manner

Authors: *B. JEYE[1], J. M. KARANIAN[1], P. P. THAKRAL[2], S. D. SLOTNICK[1];
[1]Psychology, Boston Col., Chestnut Hill, MA; [2]Ctr. for Vital Longevity, Univ. of Texas, Dallas, TX

Abstract: There is a long-standing debate as to whether recollection is a threshold/all-or-none process or a continuous/graded process. To differentiate between these two models of recollection, the shape of the receiver operating characteristics (ROC) - a plot of hit rate versus false alarm rate - can be evaluated. Specifically, a threshold model predicts a linear ROC, whereas a continuous model predicts a curved ROC. In the current functional magnetic resonance imaging (fMRI) study, we evaluated the shape of the ROC generated from activity in the hippocampus, a region known to be involved in recollection. During encoding, participants viewed abstract shapes in the left or right visual field. During retrieval, the same shapes were presented at fixation and participants classified each shape as previously in the "left" visual field or previously in the "right" visual field, followed by a three point confidence rating ("unsure", "sure", or "very sure"). To isolate neural activity associated with recollection of spatial information for the left visual field, we contrasted accurate memory for items in the left visual field (old-left-hits) versus inaccurate memory for items in the left visual field (old-left-misses). This contrast produced two activations in the hippocampus. To isolate neural activity associated with recollection of spatial information for items in the right visual field, we contrasted accurate memory for items in the right visual field (old-right-hits) versus inaccurate spatial memory for items in the right visual field (old-right-misses). This contrast did not produce any activations in the hippocampus. We also collapsed across visual field and contrasted all old-hits versus old-misses, which produced two additional activations in the hippocampus. Five-point ROCs were generated by plotting the hit rate versus false alarm rate based on the magnitude of hippocampal activity associated with each confidence rating for old-left shapes and old-right shapes ("very sure right", "sure right", "unsure right", "unsure left", "sure left", "very sure left"). The two hippocampal ROCs that differed from chance were linear and better fit by a threshold model than a continuous model. These hippocampal ROCs are distinct from behavioral ROCs, which are always curved and better fit by a continuous model than a threshold model. The present results indicate that the hippocampus operates in a threshold manner during recollection.

Disclosures: B. Jeye: None. **J.M. Karanian:** None. **P.P. Thakral:** None. **S.D. Slotnick:** None.

Poster

618. Spatial Memory

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Program#/Poster#: 618.10/V38

Topic: F.01. Human Cognition and Behavior

Support: CIHR Grant 82638

CIHR Grant 86727

CIHR Grant 230771

Title: Spontaneous use of spatial memory strategies are associated with greater cortical plasticity following a virtual spatial memory intervention program in healthy older adults

Authors: *V. D. BOHBOT[1], D. SODUMS[1], K. KONISHI[1], L. DAHMANI[1], L. BHERER[2];
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Abstract: Aim: People spontaneously use different strategies dependent on the hippocampus (HPC) and caudate nucleus (CN) when navigating in virtual environments. In previous studies, we found the use of spatial memory strategies to be associated with increased activity and grey matter in the HPC while the use of stimulus-response strategies is associated with increased activity and grey matter in the CN. While healthy aging affects grey matter in both the HPC and CN, the HPC shows an accelerated atrophy relative to other brain areas. As such, we developed a computerized spatial memory intervention program (SMIP) to specifically stimulate the HPC. This program was designed to promote the use of spatial memory strategies, taking particular attention to avoid use of stimulus-response strategies. The goal of this study was to investigate whether initial spontaneous navigation strategies affect grey matter as a result of the SMIP intervention. Methods: Healthy older adult participants (n=21) underwent the SMIP or control condition (n=33). The SMIP is comprised of 16 one-hour spatial memory training sessions administered twice a week over 8 weeks. Each participant underwent assessment of spontaneous navigational strategies with the 4 on 8 virtual maze, as well as a Magnetic Resonance Imaging scan before and after the SMIP. Results: After the SMIP, there was an increase in grey matter throughout cortex, including the frontal, parietal, temporal cortices, and bilateral HPC. Participants were categorized as responders (n=11) or non-responders (n=10) depending on whether they showed a significant increase in grey matter. As predicted, spontaneous navigation strategy significantly predicted hippocampus and cortical plasticity: 88% of spatial learners showed cortical plasticity as a result of the SMIP, as opposed to only 25% of response learners. In other words, in the responder group there were significantly more spatial learners (7/11) than in the non-responder (1/10), as determined by a chi square test ($p<0.05$). Conclusion: These results indicate the potential efficacy of a spatial memory training program at increasing HPC grey matter, and sheds further light on the relationship between navigational strategy, the HPC and its associated cortical circuits. Specifically, we showed that spontaneous spatial navigational strategies are associated with greater grey matter plasticity as opposed to the response strategy which is associated with cortical rigidity. Such evidence has substantial implications in regards

to the potential of spatial memory training programs at reducing the chances of developing memory deficits through the beneficial effect on HPC grey matter.

Disclosures: V.D. Bohbot: None. **D. Sodums:** None. **K. Konishi:** None. **L. Dahmani:** None. **L. Bherer:** None.

Poster

618. Spatial Memory

Location: Hall A

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Program#/Poster#: 618.11/V39

Topic: F.01. Human Cognition and Behavior

Support: CIHR Grant# 86272

CIHR Grant# 82638

CIHR Grant# 301763

Title: High total cholesterol and LDL-cholesterol levels are associated with decrease use of hippocampal-dependent spatial strategies

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Abstract: Aim: People can navigate in a new environment using multiple strategies, which are dependent on different memory systems. The spatial strategy is associated with increased fMRI activity and grey matter in the hippocampus while the response strategy is associated with increased fMRI activity and grey matter in the caudate nucleus. High cholesterol levels are associated with atrophy in the hippocampus and cognitive impairment in older adults. As such, in the current study we investigated the functional relationship between plasma cholesterol levels and the function of the hippocampus in humans. Specifically, we investigated the association between total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels, and navigation strategies. Methods: 139 healthy older adult participants (mean age = 65.8 ± 4.4 years) were tested in this study. Medical history pertaining to the use of cholesterol-lowering medication was obtained using a questionnaire. Participants were tested on the 4on8 virtual maze (4/8VM). The 4/8VM consists of an 8-arm

radial maze, in which 4 arms are accessible and 4 are blocked. Participants have to retrieve objects located at the end of the 4 accessible arms. Then, all 8 arms become accessible and participants have to retrieve objects now located in the 4 arms that were previously blocked. After participants have learned the task, a probe trial is given in which all landmarks are removed. On the probe trial, those that used a spatial strategy make more errors compared to those that used a response strategy because they relied on the landmarks to remember the object locations. A verbal report is administered at the end of the task to assess navigation strategy use. A subset of participants (n = 63) fasted for 12 hours and gave blood samples for lipid profiling. Total cholesterol, HDL-C, and LDL-C levels were measured from the blood samples. Results: We found that people using response strategies have significantly higher levels of total cholesterol and LDL-C levels compared to those using spatial strategies. Furthermore, cholesterol-lowering medication had a modulatory effect on navigation strategy, whereby there was a significantly higher proportion of spatial strategy users among those who take cholesterol-lowering medication. Conclusion: In the current study, we show high total cholesterol and LDL-C levels may decrease the use of strategies that are associated with increased grey matter and function in the hippocampus. These results help explain the relationship between cholesterol and cognition and may have implications for healthy aging.

Disclosures: K. Konishi: None. **R. Joober:** None. **K. MacDonald:** None. **J. Breitner:** None. **V.D. Bohbot:** None.

Poster

618. Spatial Memory

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Topic: F.01. Human Cognition and Behavior

Support: NSERC 239896-2013

Title: Common neural correlates of spatial memory and olfaction

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Abstract: Aim: In a previous study, we found that spatial memory was associated with increased fMRI BOLD activity and grey matter density in the hippocampus and medial orbitofrontal cortex, among other areas. In fact, the orbitofrontal cortex was previously shown to be involved in olfactory identification and we previously found spatial memory and olfactory identification to

be positively related. The aim of the current study was to determine whether olfactory identification and spatial memory have common structural neural correlates. Methods: We tested 58 healthy young adults on a test of olfactory identification, the Monell Extended Sniffin' Sticks Identification Test (MONEX). On this test, participants have to smell 40 sticks and have to identify the odour among four presented choices. Participants also underwent structural MRI scanning and were administered two virtual navigation tasks, namely the 4-on-8 virtual maze and the virtual town wayfinding task. In the 4-on-8 virtual maze, participants have to learn the location of 4 objects among 8 arms. In the wayfinding task, they have to learn the location of 8 landmarks in a virtual town. We used MAGeT-Brain (Multiple Automatically Generated Templates) to automatically segment and measure the volume of hippocampal subfields and extra-hippocampal white matter using multiple atlases and investigated the relationship between these volumes and navigation and olfactory performance. Results: MONEX scores positively correlated with white matter volume of the right fimbria and the left fornix. In the 4-on-8 virtual maze, faster learning was positively correlated with white matter volume in the same areas. In the wayfinding task, there was a positive correlation between the percentage of landmarks that participants were able to locate and white matter volume in the right fimbria. Conclusion: We had previously found that spatial memory performance was positively associated with olfactory identification. In the current study, we additionally show that both spatial memory and olfactory identification are related to the volume of extra-hippocampal white matter. Our results indicate that spatial memory and olfaction are related functions and that this relationship may be mediated by their common neural correlates.

Disclosures: **L. Dahmani:** None. **R. Patel:** None. **M. Chakravarty:** None. **V.D. Bohbot:** None.

Poster

618. Spatial Memory

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Topic: F.01. Human Cognition and Behavior

Support: CIHR Grant 8464

Title: Dopamine and verbal memory: the effect of an acute phenylalanine/tyrosine depletion on the word frequency mirror effect task

Authors: ***Z. K. CHAUDHARY**[1], J. THERRIAULT[2], A. DAGHER[3], M. LEYTON[4], V. D. BOHBOT[2];

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Abstract: Aim: In recognition memory, familiarity and recollection involve distinct memory processes that rely on different neural correlates. Both deficits are seen in at least some patients with Parkinson's disease (PD), but familiarity deficits develop earlier than recollection problems. It remains unclear whether either deficit reflects loss of dopamine neurons. To investigate the role of dopamine in recognition memory more directly, we tested whether decreasing dopamine synthesis in healthy volunteers would produce the pattern of performance deficits that is seen in patients with PD. Methods: Twenty healthy young adults (mean age = 24 y.o.) were tested in a within-subject, double-blind, counter-balanced, placebo-controlled experiment to lower dopamine synthesis using the acute phenylalanine/tyrosine depletion (APTD) method. Participants took part in two testing days one month apart where they ingested an amino acid mixture that was i) nutritionally-balanced (BAL), or ii) devoid of the dopamine precursors, phenylalanine and tyrosine (APTD). Performance on the word frequency mirror effect task was assessed on both days following presentation of 48 words to memorize (half high frequency (HF), half low frequency (LF)). After a delay participants classified 96 words (half old, half new) as "Remember" (conscious recollection), "Know" (familiar: no specific contextual recollection) or "New" Results: An analysis of variance revealed that there was no significant 3-way interaction between the 3 variables; test day (APTD vs. balance), word frequency (high or low) and scores (hits or false positives) previously reported in Parkinson's patients, who had elevated false alarm rates for high frequency words. A 2-way ANOVA comparing hits and false positives separately across test day irrespective of subjective Remember/Know judgments showed no main effect of test day and similar number of hits and false positives. On both days the word frequency mirror effect was replicated; there was a main of effect of word frequency (more hits to LF compared to HF words and more false positives to HF than to LF words, $F(1, 15)= 28.62$, $p<0.001$). Conclusions: We replicated the word frequency mirror effect, but this was not modulated by decreased dopamine synthesis. It is possible that an analogous performance pattern between Parkinson's and the APTD condition was not seen since the extent to which the latter lowered dopamine was less than that seen in patients ($\geq$ 80% vs. 30 to 50%). Alternatively, dopamine might not directly influence recognition memory. For example, familiarity recognition memory deficits are usually apparent only in those with additional non-dopamine related symptoms.

Disclosures: Z.K. Chaudhary: None. **J. Therriault:** None. **A. Dagher:** None. **M. Leyton:** None. **V.D. Bohbot:** None.

Poster

618. Spatial Memory

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Program#/Poster#: 618.14/V42

Topic: F.01. Human Cognition and Behavior

Title: Strategy changes across the menstrual cycle and with maternal experience in a human virtual navigation task

Authors: *D. HUSSAIN[1], S. HANAFI[2], K. KONISHI[2], W. BRAKE[1], V. D. BOHBOT[2]; [1]Psychology, Concordia Univ., Montreal, QC, Canada; [2]Douglas Mental Hlth. Univ. Inst., Montreal, QC, Canada

Abstract: Aim: A spatial or response strategy can be used to learn to navigate an environment, and these strategies depend on the hippocampus and the caudate nucleus, respectively. In rodents, high estradiol (E2) has been shown to bias females to use a spatial strategy while low E2 is associated with response strategy use (Korol et al., 2004; Quinlan et al., 2008). However, this effect disappears with reproductive experience (Hussain et al., 2013). In women, steroid hormones vary over the course of the menstrual cycle such that E2 peaks during the second half of the cycle (i.e. the luteal phase). Furthermore, the high E2 phase of the menstrual cycle is associated with an increase in hippocampal grey matter (Protopescu et al., 2008). We therefore hypothesized that women tested during the luteal phase would be more likely to use a spatial strategy on a virtual navigation task, and that this difference would no longer be observed in mothers. **Methods:** Fifty-four young women with (n = 28) and without (n = 26) maternal experience (ages 23-36 years) were tested either during the follicular (n = 23) or luteal (n = 31) phase of the menstrual cycle on the 4-on-8 virtual maze (4/8VM). The 4/8VM consists of an 8-arm radial maze, in which 4 arms are open and 4 are blocked. Participants have to retrieve objects located at the end of the 4 open arms. Then, all 8 arms are open and participants have to retrieve objects now located in the 4 previously blocked arms. Strategy use is assessed with a verbal report and a probe trial in which all landmarks are removed, leading to impaired performance in spatial learners. **Results:** Consistent with our hypothesis, it was found that women tested in the luteal phase predominantly used a spatial strategy (64.5%), whereas the opposite pattern was observed in the follicular group (spatial = 30.4%; X^2 = 6.14, p = .013). Contrary to our hypothesis, this pattern was also observed in women with maternal experience (X^2 = 5.04, p = .025). In addition, non-mothers needed more trials to reach criterion in the luteal than in the follicular phase, whereas the opposite pattern was observed in mothers ($F_{(1,50)}$ = 6.38, p = .015, η^2 = .113). **Conclusion**: These findings suggest that women tend to use a spatial strategy when tested during the luteal phase whereas they tend to use response during the follicular phase, and this occurs with and without maternal experience. This indicates that multiple memory system bias changes with fluctuating E2 levels across the menstrual cycle; however, unlike in rodents, this does not change with reproductive experience.

Disclosures: **D. Hussain:** None. **S. Hanafi:** None. **K. Konishi:** None. **W. Brake:** None. **V.D. Bohbot:** None.

Poster

618. Spatial Memory

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Topic: F.01. Human Cognition and Behavior

Support: Department of Veterans Affairs Clinical Science Research and Development Service.

Title: Does the hippocampus keep track of time?

Authors: *D. J. PALOMBO[1,2], M. M. KEANE[3,2,1], M. VERFAELLIE[2,1];
[1]Psychiatry, Boston Univ. Sch. of Med., Boston, MA; [2]VA Boston Healthcare Syst., Boston, MA; [3]Psychology, Wellesley Col., Wellesley, MA

Abstract: In the present study, we examined the role of the medial temporal lobe (MTL) in prospective time estimation at short and long timescales using a novel behavioral paradigm adapted from rodent work. Amnesic patients with MTL damage and healthy control participants estimated the duration of nature-based video clips that were either short (less than or equal to 90 seconds) or long (more than four minutes). Consistent with previous work in rodents, we found that amnesic patients were impaired at making estimations for long, but not for short durations. Critically, these effects were observed in patients who had lesions circumscribed to the hippocampus, suggesting that the pattern observed was not attributable to the involvement of extra-hippocampal structures. That the MTL, and more specifically the hippocampus, is critical for prospective temporal estimation only at long intervals suggests that multiple neurobiological mechanisms support prospective time estimation.

Disclosures: **D.J. Palombo:** None. **M.M. Keane:** None. **M. Verfaellie:** None.

Poster

618. Spatial Memory

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NIH R21NS087527 (Ekstrom)

NIH R01NS08402 (Gurkoff)

Title: Damage to the medial temporal lobes impairs spatial precision and spatiotemporal binding while sparing allocentric memory

Authors: *B. KOLARIK[1,2], K. SHAHLAIE[3], A. HASSAN[2], A. BORDERS[1], K. KAUFMAN[1], G. GURKOFF[3], A. YONELINAS[1], A. EKSTROM[2];
[1]Univ. of California, Davis, Davis, CA; [2]Ctr. for Neuroscience, Univ. of California, Davis, Davis, CA; [3]Departmento of Neurolog. Surgery, Univ. of California Davis, Sacramento, CA

Abstract: Separate lines of research suggest roles for the human hippocampus in both spatial navigation and the binding of item and context information in episodic memory. Reconciling these two accounts has proven difficult. Here, we tested a novel model of hippocampal function termed the precision and binding model (PBM) (Yonelinas, 2013), which postulates roles for the hippocampus in complex, high-resolution binding as part of a larger role in both spatial navigation and episodic memory. Using a virtual analogue of the Morris Water Maze (vMWM), we tested a patient with damage to the medial temporal lobes (MTL) on multiple target locations. We analyzed search patterns on probe trials using a sliding window centered on the target rather than employing spatial quadrants, as done in past work, to better test for deficits in spatial precision. Analysis of patient search patterns during probe trials revealed a tendency to search in the vicinity of the hidden platform although with less spatial precision than controls. These data suggest some sparing of allocentric spatial memory in patients with MTL damage but that the precision of this memory is reduced relative to controls. To further characterize the precision deficit we used a curve fitting analysis to model the accuracy of the search trajectories for the patient and the lowest performing half of our control sample. This analysis revealed that control performance was best fit with a second-order function indicating precise memories for the target location even at the smallest analysis window. In contrast, patient performance required a third parameter to capture the steep drop in precision as the analysis window decreased in size. These results highlight the severe precision deficit the patient displayed relative even to the worst

performing controls. Additionally, we show that memory and precision impairments become more severe when the patient was required to remember more than one target location, suggesting deficits in spatiotemporal binding. Together, our findings suggest a role for the hippocampus in spatial precision and spatiotemporal binding, consistent with the PBM model.

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Poster

618. Spatial Memory

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Topic: F.01. Human Cognition and Behavior

Support: NIMH Grant MH083734

Title: High-resolution hippocampal activation patterns predict memory precision

Authors: *A. A. BORDERS[1], J. D. STOKES[1,2], C. T. KYLE[2], A. D. EKSTROM[1,2], A. P. YONELINAS[1];
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Abstract: The human hippocampus is widely known to support human episodic memory, however, recent evidence suggests that the hippocampus may serve a more specific role in insuring the encoding and retrieval of precise details and associations of memories during both episodic and working memory tasks (Yonelinas, 2013). In contrast, surrounding regions in the medial temporal lobe (MTL), e.g. parahippocampal cortex, are thought to support comparable memory processes using coarse, less precise representations. However, given the complex connectivity profile within the MTL, it seems likely that dynamic interactions between subregions within the MTL act together to support a range of memory precision, ultimately predicted by task demands. To explore these network dynamics, we collected high-resolution functional images of the MTL during an associative recall task. Participants were presented with a location on a circle followed by a unique word and asked to memorize the pair. At retrieval, a studied word was presented and the participant used a mouse to indicate the precise recalled location paired with the word. This allowed for assessment of precision-evoked activation during encoding and retrieval. Participants were also asked to rate their confidence regarding their accuracy on each trial. Results showed that cortical areas in the medial temporal lobe were involved during the retrieval of the word-location pairs, but activity in these regions did not

differentiate between precise and coarse retrieval responses. In contrast, patterns of activation within the hippocampal subregions predicted increased memory precision and memory confidence.

Disclosures: **A.A. Borders:** None. **J.D. Stokes:** None. **C.T. Kyle:** None. **A.D. Ekstrom:** None. **A.P. Yonelinas:** None.

Poster

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R21NS087527

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R01NS08402

Title: Dynamic spatiotemporal organization of individual episodic memory retrieval networks

Authors: ***A. SCHEDLBAUER**[1], A. WATROUS[2], C. KADIPASAOGLU[3], N. TANDON[3], A. EKSTROM[1];
[1]Univ. of California, Davis, Davis, CA; [2]Univ. of Bonn, Bonn, Germany; [3]Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX

Abstract: Past work has suggested that increases in functional connectivity characterize successful episodic memory retrieval, as measured through phase consistency between distal electrodes in electrocorticography (ECoG) patients and beta time-series correlations in healthy participants undergoing functional magnetic resonance imaging (fMRI). However, multilobular ECoG recordings, in addition to offering excellent regional coverage, also offer superior temporal resolution. Capitalizing on both the superior spatial and temporal resolution of ECoG, we investigated whether the evolution of specific network configurations might also be predictive of correct episodic memory retrieval. We hypothesized that the single-trial evolution of networks underlying correct memory retrieval would involve lower variability in node connectivity compared to incorrect retrieval. Patients performed an episodic memory task in which they freely navigated a virtual environment and encoded spatiotemporal contextual details.

Those who performed above chance were able to remember information regarding spatial and temporal distances between landmarks visited during navigation. Adapting pairwise phase consistency (PPC: Vinck et al. 2010) for single trial estimates, we replicated our earlier findings of greater connectivity for correct versus incorrect retrieval but at the single trial level. We then employed the global variability coefficient (GVC: Cole et al. 2013) to assay variability in connectivity across nodes while simultaneously controlling for differences in connectivity between the two networks. We found overall lower GVC in the correct compared to the incorrect network, indicating a more stable pattern of connectivity over time within the correct retrieval network. Our findings suggest that changes in the configurations of networks of interacting brain regions can provide novel insight into whether memory retrieval will succeed or fail, even on a single trial.

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Poster

618. Spatial Memory

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R21NS087527

R03NS093052

R01NS08402

Title: Integration of familiar and novel spatial templates in episodic memory

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[1]Ctr. for Neurosci., UC Davis, Davis, CA; [2]Ctr. for Neurosci., [3]Univ. of California, Davis, Davis, CA

Abstract: Theoretical models of hippocampal function suggest its involvement in both the encoding and retrieval of familiar representations (e.g., spatial context information) as well as the rapid encoding and retrieval of novel episodic events. Yet an important and unsolved question regards how exactly the hippocampus integrates new episodic information with existing cortical

representations, for example, encoding a new event in a familiar geometry (e.g., visiting a new town that has a square-like spatial layout). In a previous study, we demonstrated that CA3/DG showed reductions in pattern similarity in response to changes in spatial context. In contrast, the CA1 subfield, historically considered a major output junction of the hippocampal formation, showed prominent increases in pattern similarity during the processing of salient shaped configurations (i.e. circle or square-shaped) compared to less distinctive configurations (i.e. morphed shapes) (Stokes, Kyle and Ekstrom, 2015). Due to the high familiarity of both shapes in the paradigm (circle and square), the extent to which integration of spatial context depends upon existing vs. novel shape templates, remains an open question To address this, prior to scanning, participants underwent extensive pre-training on irregular, novel shapes. While undergoing high-resolution fMRI targeting the hippocampus, participants processed videos of spatial environments involving the trained shape, a completely novel untrained shape, and an intermediate morph shape. Similar to our past work, participants indicated whether the environment represented in the video they had just seen was the same or different from the previous video. We predicted that CA3/DG would show pattern similarity effects that differ as a function of environmental similarity, despite the fact that these shapes were completely novel to participants. Our preliminary findings support this prediction, showing that CA3/DG serves a role in discriminating changes in spatial context during the formation of novel spatial representations, specifically during periods involving overlapping sensory information. Our second prediction involved CA1, in which we anticipated higher pattern similarity for the trained compared to untrained shape, consistent with its hypothesized role in integrating new information within the hippocampal circuit. Preliminary results suggest that CA1 shows higher sensitivity to trained templates when compared to untrained templates. Overall, these findings suggest that the interplay between novel sensory inputs and prior experience are supported by unique contributions in hippocampal subregions.

Disclosures: **J. Stokes:** None. **C. Kyle:** None. **A. Ekstrom:** None.

Poster

618. Spatial Memory

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NIH Grant R01NS08402

Title: A tale of two temporal retrieval strategies: dynamic expression of temporal sequence retrieval

Authors: *J. S. LIEBERMAN, C. T. KYLE, J. D. STOKES, A. D. EKSTROM;
Ctr. for Neurosci., Univ. of California Davis, Davis, CA

Abstract: Episodic memories depend on accurate retrieval of temporal details underlying specific events. Past research suggests that participants can use two fundamentally different retrieval mechanisms for retrieving the order of temporal events, one involving a recency strategy ("which object came before another object?") and the other involving an associative strategy ("were the two objects the same distance from a third object?"). Yet the neural basis for retrieving temporal information using these two strategies remains unclear. To address this, participants learned two unique sequences of objects, then performed two versions of a temporal order judgment task during whole-brain fMRI. In both versions, on each 6-s trial, participants were visually presented with 3 objects (1 target and 2 probes) and asked to make judgments about the relative positions of the objects within the list order via a button press. However, the type of judgment made was unique to each version and required participants to use a distinct retrieval strategy. In version 1 (the "chaining" task), participants used an associative recall mechanism ("are the two probes the same distance from the target?"). In version 2 (the "distance" task), participants used a temporal distance/recency judgment as the recall mechanism ("which of the two probes is closer to the target?"). We predicted that, despite the similarities in visual input and encoding, we would see differences in the brain networks involved in retrieval using the two strategies. We used univariate analyses to examine brain regions that were unique to one strategy or common to both strategies. Preliminary results showed that both mechanisms recruited the bilateral hippocampus and bilateral visual cortex, consistent with prior research. Associative retrieval, however, showed significantly greater activation than the distance task in the parietal lobe, including the right superior parietal lobule and bilateral supramarginal gyrus. In contrast, recency-based retrieval showed greater activation in the frontal and temporal lobes compared to associative retrieval, including the bilateral parahippocampal gyrus, bilateral superior temporal gyrus, and left and midline medial prefrontal cortex. In contrast to past results, which have generally conceived of retrieval involving a unitary network of brain areas ("retrieval network"), our findings show that how information is accessed during retrieval can involve fundamentally different networks of brain areas. They further argue that while temporal retrieval involves some common brain areas, recruitment of unique brain networks may be critical to how we access temporal information.

Disclosures: J.S. Lieberman: None. **C.T. Kyle:** None. **J.D. Stokes:** None. **A.D. Ekstrom:** None.

Poster

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Title: Low frequency hippocampal oscillations differentiate between successful retrieval of related versus unrelated spatiotemporal context

Authors: *M. COPARA[1], K. KIM[3], M. ROLLO[3], C. KADIPASAOGLU[3], N. TANDON[3], A. EKSTROM[2];
[2]Psychology, [1]UC Davis, Davis, CA; [3]Univ. of Texas, Hlth. Sci. Ctr. at Houston, Houston, TX

Abstract: Current evidence strongly supports the central involvement of the hippocampus (HPC) in storing and retrieving memories for recent events. However, a critical question regards exactly how the HPC represents the 'when and where' of an event memory. Recently, we showed that HPC represents unrelated spatiotemporal information by decreasing pattern similarity across contexts, which we determined using multivoxel pattern similarity (MPS) and high-resolution functional magnetic resonance imaging (fMRI). Another candidate mechanism for storing and retrieving different vs. similar events involves frequency multiplexing, which may relate to the recruitment of distinct vs. overlapping ensembles depending on the frequency of interactions (e.g., Watrous and Ekstrom,, 2014). To address how this occurs on the fast time scale characterizing neural events, we employed intracranial electroencephalography in patients undergoing seizure monitoring while they retrieved either related or unrelated spatial and temporal contexts from a virtual reality spatial navigation task. Our preliminary findings show that there are significantly more electrodes showing greater spectral power in spatial retrieval than temporal retrieval for unrelated spatiotemporal context whereas related spatiotemporal context showed less of a difference between spatial and temporal conditions. This suggests that when patients retrieve unrelated spatial and temporal contexts, there is more neural

differentiation in the hippocampus compared to when patients retrieved related contexts and this may be an important mechanism that the hippocampus utilizes to differentiate spatiotemporal contexts.

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Poster

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Title: Hippocampal low-frequency oscillations elicited during virtual navigation persist in the absence of visual and self-motion cues

Authors: *L. K. VASS[1], M. S. COPARA[1], M. SEYAL[2], K. SHAHLAIE[3], S. TOMASZEWSKI FARIAS[2], P. Y. SHEN[4], A. D. EKSTROM[5];
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Abstract: Low-frequency (delta/theta band) oscillations have been observed during spatial navigation in both rodents and humans, but the conditions required to elicit these oscillations in humans remain controversial. Whereas some theories propose that hippocampal low-frequency oscillations are primarily generated in response to sensorimotor input, others propose that these oscillations can be driven by internally-generated memory processes. To adjudicate between these possibilities, we recorded intracranial hippocampal EEG activity in patients undergoing seizure monitoring while they explored a virtual environment. Critically, this environment contained teleporters, which allow the patient to experience movement through space in the absence of visual (i.e., optic flow) and self-motion (e.g., vestibular, proprioceptive) cues. If low-frequency oscillations are driven solely by visual or motoric exploration of an environment, then

these oscillations should attenuate once the patient enters the teleporter. To test for this possibility, we used the oscillatory detection method P_episode to quantify the proportion of time low-frequency oscillations were present during the task. We then compared the percent time in an oscillatory state immediately prior to teleportation when patients virtually navigated in the presence of visual information to the percent time in an oscillatory state during the teleportation period. Preliminary results indicate that hippocampal low-frequency oscillations are sustained during teleportation and do not differ significantly in prevalence between visual-motor movement and teleportation periods. In contrast, higher-frequency oscillations in the beta and gamma bands were modulated by these teleportation events. These results suggest that low-frequency hippocampal oscillations can be driven by internal mechanisms and do not require visual or self-motion cues to persist.

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Poster

618. Spatial Memory

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Title: Temporal encoding strategies produce comparable boosts in free recall performance to spatial encoding strategies

Authors: ***N. R. BOUFFARD**, J. STOKES, C. KYLE, J. LIEBERMAN, A. EKSTROM; Univ. of California, Davis, Davis, CA

Abstract: The method of loci is a highly effective mnemonic technique that recruits existing salient memory for spatial locations and uses this information as a scaffold for remembering a list of items (Yates, 1966). By mentally pairing each spatial locus with a list item, the list is more likely to be recalled, and in the same order as it was presented (Bower et al., 1970; Roediger et

al., 1980). One possible account for the effectiveness of the spatial method of loci comes from the perspective that it utilizes evolutionarily preserved mechanisms for spatial navigation within the hippocampus (Macguire et al., 2003). Recently, though, neurons coding temporal features have also been described in the hippocampus (Mauk et al., 2004; Meck et al., 2013), challenging the primacy of spatial-based functions to hippocampal processing. Given the presence of both spatial and temporal coding mechanisms within the hippocampus, we predicted that temporal coding strategies might also enhance memory. In the current study, we had participants learn lists of unrelated nouns using a spatial method of loci (using the layout of their home as the scaffold) or a temporal method of loci (using autobiographical life events as the scaffold). We then tested their memory for the lists with a free recall task. As predicted, participants learned the lists the fastest when implementing the spatial method of loci compared to other strategies that participants spontaneously used prior to instruction at the beginning of the study. The temporal method also improved participants list learning speed compared to the uninstructed strategies, but not to the extent of the spatial method, which we attributed to the initial difficulty in using autobiographic events to remember list items. Participants also completed a delayed recall task at the end of the study where they were asked to recall all of the lists they had learned. We found that words learned using temporal and spatial methods were more likely to be recalled than words learned using other strategies. Importantly, we found no significant difference in delayed recall performance between the spatial and temporal methods. These results suggest that although the temporal method of encoding we employed may require more trials to master than a spatial one, temporal representations can produce comparable boosts in memory performance to spatial methods during free recall.

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Poster

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Wallenberg Network Initiative on Culture, Brain, and Learning

University of Pennsylvania and John Templeton Foundation Project on Prospection Psychology

Title: Prospective representation of navigational events in the human hippocampus

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Abstract: The mental representation of future states is a critical component of goal-directed behavior. The hippocampus and neighboring medial temporal lobe (MTL) cortices are believed to play a critical role in spatial navigation through representation of goal locations (McKenzie et al., 2013) and prospective location coding (Johnson and Redish, 2007), and by supporting goal-directed route planning (Brown et al., 2014; Hartley et al., 2003). Using whole-brain high-resolution functional magnetic resonance imaging (hr-fMRI), we examined whether the human MTL supports goal-directed navigation by representing future goal states during initial navigational planning. On day 1, thirteen healthy, right-handed young adults learned to navigate to hidden goal locations in a virtual circular track environment. Each location was uniquely associated with a distinct pair of fractal images. On day 2, participants repeatedly navigated to the goals during hr-fMRI scanning. Participants began each trial at a familiar location, after which the environment was hidden from view and participants were cued by of one of the fractals to plan navigation to its location. Participants subsequently navigated to this goal. Using multivoxel pattern analyses (MVPA), results demonstrate that hippocampal patterns of activity contain information during initial planning that codes the goal location to which participants will subsequently navigate. Moreover, when navigating to a distal location, classifier evidence for intervening locations along the route is greater than evidence for other non-goal locations. Hippocampal evidence for the future goal is correlated with that of an interconnected neocortical network, including MTL cortex and retrosplenial cortex. Collectively, these results suggest that the human hippocampus and related cortical structures prospectively represent future goal states, and support mental route simulation facilitating flexible planning of navigation behavior.

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Poster

618. Spatial Memory

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Title: Temporal features of narrative construction are different for healthy older adults and patients with hippocampal damage

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Abstract: Patients with damage to the hippocampus have sometimes been reported to be impaired at both remembering the episodic past and imagining the episodic future. Studies in this literature have counted the number of episodic and semantic details given when participants constructed narratives about remembered and imagined events. However, analyses based on detail counts alone do not allow for inference into what aspects of narrative construction may change as a result of hippocampal damage. Our study followed a procedure developed by Race et al. (2011) in which a time limit was imposed on narratives and minimal probe questions were used. We tested patients with hippocampal lesions (n=7) and found that their narratives from the near past contained fewer details than did those of controls (but this was not the case for narratives about the remote past). Total detail counts were also similar to controls in both the near and distant future. However, analysis of the temporal dynamics of narrative construction revealed differences between the patients and controls in all time periods (even when the number of details was similar for the two groups). Controls produced narratives that were longer and more variable in duration than the narratives produced by patients. Controls produced details slowly at the beginning of their narratives but increased their speed of detail production later in their narratives. Patients exhibited the opposite pattern. In addition, controls produced more semantic information at the beginning of their narratives and more episodic information later in their narratives. Again, patients exhibited the opposite pattern. These results suggest that patients with hippocampal damage are capable of remembering richly detailed episodic past events and imagining richly detailed future events. Despite their ability to produce narratives that are richly detailed, patients with hippocampal damage still exhibited changes in their narrative structure in comparison to controls, suggesting that some aspects of narrative construction were affected by hippocampal damage. We suggest that the changes in the narrative structure of the patients may reflect the consequences of their deficit in anterograde memory.

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Poster

618. Spatial Memory

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Program#/Poster#: 618.26/W6

Topic: F.02. Animal Cognition and Behavior

Title: "Global-first" topological properties pattern recognition in rodent

Authors: *X. LIU, Z. ZHOU, N. LIU, Y. TANG, L. WANG;
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Abstract: "Global-first" topological properties pattern recognition in Rodent Xue-Mei LIU[1], Zheng ZHOU[1], Nan LIU,Yong-qiang TANG, Li-Ping WANG[1]* *[1]Shenzhen Key Lab of Neuropsychiatric Modulation, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China* *Correspondence: Li-Ping WANG, PhD & MD, lp.wang@siat.ac.cn **Abstract:** "Global-first" topological approach, is one of the crucial theories in primitive visual perception. Previous systematic evidence has showed that human and several animal models possess topological perception, yet the detail mechanism of this perception is poorly understood. To dissect neural circuits of topological recognition, we need simpler and more accessible animal models. Here, we designed two experimental models, trained by foot shock or food rewarding, to detected whether rodent possess topological perception. The results showed that the mice could discriminate the topological different patterns, with random choice to topological equivalent patterns. And we also demonstrated that the rats were sensitive to topological difference, but were insensitive to topologically equivalent patterns. We concluded that mice and rat both possess the ability of topological pattern recognition, thus, the models provided us a model to study the neural substrates of topological perception. **Keywords:** Topological perception; rodent;

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Poster

619. Language III

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Program#/Poster#: 619.01/W7

Topic: F.01. Human Cognition and Behavior

Title: Decomposing the bilingual language control network into preparatory processes and execution

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Abstract: Bilingual language control is complex because bilinguals must select contextually appropriate words and rules to communicate in a dynamically changing target language (TL). In a recent meta-analysis, Luk et al. (2012) described 7 regions involved in bilingual language control. The majority of the paradigms investigated conflate preparatory processes (i.e., the cue indicating TL) with the execution of a task. To better understand the functions of these 7 regions, we created a paradigm where participants were instructed to use a TL by using a non-linguistic cue (# or *) before the presentation of any word on which to execute the desired operation on. To compare the processes involved in preparing to use a TL to those involved in preparing to execute a grammatical rule, a second preparation phase presented one of four grammatical rules. Afterward, participants received word stimuli in the TL of interest and were asked to mentally manipulate them according to the rule indicated. The task was subject-paced with jittered spacing between phases, allowing for the separate estimation of each phase. fMRI data were acquired from 23 early Spanish-English bilinguals. 7 spherical ROIs were defined based on the meta-analysis reported, and mean beta weights were extracted for each ROI. 3 (task phase) x 2 (TL) ANOVAs were run on each of the 7 ROIs independently, and a main effect of task phase was found for all regions. Based on the patterns of results found in the follow-up analysis, three functional sub-networks were identified. The first, a “Preparatory Network” involved the right prefrontal cortex only. This region was primarily active during the Prepare TL phase, and may be involved in inhibition. The second sub-network was identified as the “Language Tracking” network and consisted of the right caudate nucleus, left inferior frontal gyrus (BA47), and left middle temporal gyrus. This network was equally active during the Prepare TL and Execute phases, but was more active in these phases than during the Prepare Grammar phase. The fact that this network did not activate as strongly when preparing to execute grammatical rules suggests that this circuit is recruited to control TL rather than language processing in general. The final “Execution Network” consisted of regions that were more active during rule execution than in any preparatory process, and included the left middle frontal and superior frontal gyri, and Broca’s area, which is central to grammatical processes. The identification of these three circuits further reveals how each of the previously defined bilingual language control regions are involved in the preparation and execution of TL specific processes in the bilingual brain.

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Poster

619. Language III

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Topic: F.01. Human Cognition and Behavior

Support: NIH Grant NS042867

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Title: Analysis of hemispheric differences in gene expression in primates

Authors: *A. VERENDEEV[1], G. MUNTANÉ[3], T. M. MAYNARD[2], C. C. SHERWOOD[1]; [1]Dept. of Anthrop., [2]Dept. of Pharmacol. and Physiol., George Washington Univ., Washington, DC; [3]Inst. de Biologia Evolutiva, Univ. Pompeu Fabra - CSIC, Barcelona, Spain

Abstract: Language and handedness are two examples of asymmetrical brain function in humans. Although these behaviors have been well characterized in their neurobiology and neuroanatomy, their genetic underpinnings have not been explored in much detail. Using qPCR, we assessed hemispheric differences in gene expression in rhesus macaque (*M. mulatta*, n=5) and humans (n=5) in genes previously associated with language and handedness (*pcsk6*, *mns1*, *gli3*, *mgrn1*, *foxp2*, *kiaa0319*, *lefty1*, *nodal*, *drd4*, and *ccdc78*). Overall, we found no evidence of differential expression between the two hemispheres among the genes examined. However, *kiaa0319*, a gene implicated in dyslexia in humans, showed a very pronounced lateralization in its expression with a strong leftward bias. *Foxp2*, on the other hand, did not differ in its expression between the two hemispheres in either species.

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Poster

619. Language III

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Topic: F.01. Human Cognition and Behavior

Title: Developmental changes in the functional and structural connectivity within brain networks involved in phonological processing

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Abstract: We investigated concomitant developmental changes in structural and functional connectivity in the neural language networks of Chinese children and adults with DTI and PPI analyses. We investigated functional connectivity in the language network during an auditory rhyming task using PPI between four left hemisphere regions: inferior frontal gyrus (IFG), superior temporal gyrus (STG), inferior parietal lobule (IPL), and middle occipital gyrus (MOG). We examined structural connectivity by using DTI tractography to reconstruct three left-hemisphere tracts associated with language (arcuate fasciculus, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus). Tractography analysis revealed that the investigated fascicles had differential developmental trajectories that correlated with PPI values. In particular, the arcuate fasciculus showed a steady increase in fractional anisotropy (FA) across age with higher FA in fifth-graders than third-graders and higher FA in adults than in fifth-graders. In contrast, the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus showed relatively late FA increases with higher FA in adults than in children but no difference between third-graders and fifth-graders. PPI analysis revealed only one significant developmental change; which is the increased connectivity from MOG to STG, suggesting greater integration of orthographic information in phonological processing in adults. Correlation analysis between PPI and DTI found that, within children, PPI connectivity from STG to both IPL and IFG were positively correlated with FA in arcuate fasciculus. This suggests that functional connectivity in the anterior language network relies on the development of the underlying arcuate fasciculus in elementary school years. We also found that, within adults, PPI from STG to MOG was positively correlated with FA in inferior longitudinal fasciculus and inferior fronto-occipital fasciculus, and that PPI from MOG to STG was positively correlated with FA in inferior longitudinal fasciculus. It suggests that the late matured long-range fiber tracts play an important role in supporting the posterior language network involving orthographic representations in adults. Finally, we found that FA in inferior longitudinal fasciculus was negatively correlated with PPI from STG to IFG in adults, suggesting that there may be a developmental shift from anterior to posterior language network in phonological processing in Chinese adults; which may be driven by literacy acquisition.

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Poster

619. Language III

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Intramural Research Program of the National Institute of Mental Health, NIH/DHHS

Title: Impaired articulation but unimpaired auditory processing in KE family members with mutation of FOXP2

Authors: K. SCHULZE[1], L. HALLIDAY[2], S. AMITAY[3], F. VARGHA-KHADEM[1], *M. MISHKIN[4];
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Abstract: Background Half the members of the KE family (affected family members, aKE) suffer from an inherited neurodevelopmental speech impairment caused by the mutation of the FOXP2 gene. The core problem underlying this impairment has been identified as an orofacial and verbal dyspraxia, a higher order oromotor deficit that manifests most prominently as an articulatory disorder (Vargha-Khadem et al, 2005). Aim The primary objective of the present study was to determine whether there might be an additional core deficit, viz., an impairment in auditory processing associated with aKE's speech difficulties. Methods To compare auditory processing in aKE (n = 7), unaffected KE family members (uKE, n = 3), and controls (n = 13), we employed complex listening tasks that measure the ability to process the temporal and spectral aspects of auditory information (Tone detection in quiet, Amplitude modulation, Backward masking, Simultaneous masking, Frequency modulation detection, Frequency discrimination, Tone detection in noise). Results There was a significant effect of group for Frequency discrimination ($p = 0.007$, corrected α-level = 0.005), but this was due to a significantly lower, thus better, frequency discrimination threshold in the aKE compared to controls ($p = 0.001$, corrected α-level = 0.017). No other psychoacoustic tests yielded a significant group effect. Conclusions Our results suggest that the aKE's FOXP2 mutation does not interfere with auditory processing and, conversely, that auditory processing difficulties do not contribute to the aKE's articulation impairment. REFERENCE Vargha-Khadem et al. (2005). FOXP2 and the neuroanatomy of speech and language. Nat Rev Neurosci, 6, 131-138.

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Poster

619. Language III

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Program#/Poster#: 619.05/W11

Topic: F.01. Human Cognition and Behavior

Title: Deciphering the role of CNTNAP2 in cognitive disorders; from molecule to patient

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Abstract: Investigations into CNTNAP2 are of high interest as disruptions in this gene are involved in a range of cognitive disorders including autism. CNTNAP2 is expressed across a number of brain regions including the cortex, striatum and thalamus, recapitulating the circuitry known to modulate higher order cognitive processes, suggesting an important role of CNTNAP2 in brain development. Furthermore, molecular links with FOXP2 suggest that CNTNAP2 may be involved in language related pathways. Given the range of phenotypes produced by CNTNAP2 disruption and the early and widespread expression pattern of its protein product CASPR2, it is likely that this gene has multiple roles in the brain, however these remain poorly understood. We are investigating CNTNAP2 at a phenotypic and molecular level to understand its function in the developing and adult brain, and why mutations in CNTNAP2 lead to specific neurological phenotypes. Patient studies reveal a complex relationship between genotype and phenotype. CNTNAP2 is located on 7q35 and spans 2.3 Mb, making it a large physical target for disruptive mutations. Accordingly a large number of mutations have been identified at the CNTNAP2 locus in patients with a range of cognitive phenotypes that often include intellectual disability (ID) and epilepsy. We compared novel patients with previously reported individuals harboring CNTNAP2 mutations and found complex phenotypic profiles of varying severity in patients with heterozygous mutations. Furthermore heterozygous changes were also found in unaffected individuals, suggesting that mutation of a single copy of CNTNAP2 is not fully penetrant. By contrast, detailed phenotypic analysis of patients with homozygous CNTNAP2 loss revealed a syndromic disorder characterised by severe intellectual disability, early-onset drug-resistant

epilepsy, reduced or absent language, communicative impairments and autism. Further phenotypic and molecular investigations into these patients will be essential for identifying the core effects of CNTNAP2 in cognitive disorder. We are currently investigating the properties of normal and mutant CNTNAP2 to understand the molecular function of CASPR2 and how these variants give rise to cognitive phenotypes. These molecular screens will not only shed light into the contribution of CNTNAP2 variants to complex neurodevelopmental disorders such as epilepsy, autism and language impairment, but also further our understanding of the role of CNTNAP2 in normal brain development.

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Title: Rapid learning and consolidation of novel morphosyntax in human neocortex: neuromagnetic evidence

Authors: *A. LEMINEN[1], L. KIMPPA[3], M. LEMINEN[2], M. LEHTONEN[4], J. P. MÄKELÄ[5], Y. SHTYROV[2];
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Abstract: Research into neurobiological mechanisms of morphosyntactic processing of language has suggested specialized systems for decomposition and storage, which are used flexibly during the processing of both inflections (e.g., boy+s, boy + plural marker) and derivations (boy+ish, boy plus attenuator), the main morphological tools humans use to change and create words.

However, the neural underpinnings of acquisition of novel morphology are still obscure. We investigated the role of semantic information in morphosyntactic affix learning and the role of overnight consolidation in the formation of neural memory traces for new affixes. First, participants were implicitly trained on a subset of novel affixes combined with real word stems (not included in the actual experiment) by listening to and reading these novel combinations presented with respective pictures (e.g. cup-ku = small cup). After the training session, the participants had to report the meaning of the novel suffixes, following which their neuromagnetic brain responses were acquired using MEG. The participants passively listened to the newly trained suffixes presented with either real word or pseudoword stems, or similar items that included previously untrained affixes (counterbalanced across participants). The MEG recording (but not training) was repeated again after a one-night sleep using the same stimuli, to test the effects of overnight consolidation. Analysis of event-related fields showed that on Day 1, as early as 50 ms after the suffix onset, novel suffix combined with real stems, elicited significantly larger responses than pseudostem+novel suffix combinations, regardless of whether the suffixes were trained or untrained, implying a robust activation of a memory trace for the known stem but not yet the new affix. On Day 2, these differences disappeared, suggesting the consolidation-related enhancement of the memory traces for the newly learned suffixes and/or complex words. At the later processing stages (~120ms), there was an increase in the magnitude of the responses on Day 2, also indicating an overnight consolidation of memory traces for novel complex combinations. The neural source reconstruction showed the increase of activation in bilateral fronto-temporal cortical generators, particularly for trained suffixes, suggesting that these areas underpin the formation of novel neural memory trace the novel derivational endings. Overall, the results demonstrate the rapid and dynamic processes of build-up and consolidation of neocortical memory traces, taking place as a result of a short period of exposure to novel morphology.

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Poster

619. Language III

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Title: Automatic processing of morphosyntax by second language learners

Authors: *L. A. HEDLUND[1], A. LEMINEN[2], S. HUT[1], L. KIMPPA[1], M. LEMINEN[2], Y. SHTYROV[3];
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Abstract: In our surroundings, we often encounter complex things, comprised of multiple subparts. A striking example of such a complexity is offered by language. Many words are complex, i.e. they have more than one meaningful element (=morpheme), e.g., boy-s, boy+plural marker (inflection); boy-ish, boy+attenuator (derivation). Recent MMN findings (Leminen et al., 2013, Cortex) have shown that the brain automatically processes native language (L1) inflections by decomposing them into morphemes, while derivations are likely to form unitary representations. However, little is still known about the brain mechanisms responsible for the processing of complex words in a second language (L2). To investigate this issue, we presented beginning and advanced L2 learners and L1 speakers of Finnish with a balanced set of inflected and derived words and complex pseudowords (real stem+pseudosuffix), while recording EEG in a passive multifeature paradigm. L1 speakers replicated the morphological MMN pattern that showed stronger responses for derived than for inflectional words, indicating the existence of full-form memory traces for derivations and decompositional parsing for inflected forms. Crucially, neither beginning nor advanced L2 learners showed such an effect, suggesting weaker memory circuits for L2 derived words and thus likely automatically decompose them into stem and suffix, similar to inflections. All groups showed a syntactic ERP pattern - a stronger response to pseudowords than to real words. We show that morphological parsing takes place already early on in L2 grammar learning, and even advanced L2 learners seem to continue using the parsing route for all types of morphological complexities.

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Poster

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Support: PICT2013-0718

Title: What was that word? Selective interference during memory consolidation of novel words in adults

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Abstract: We analyzed the role of memory consolidation in the acquisition of novel words using an interference procedure. We separately studied the effects of interference in the aspects of word form (phonology and orthography) and the semantic content. Participants learned 9 nonwords, visually presented, associated with a picture and a definition. A short term memory test was performed 5 min after learning, and a long term memory test took place 48 h after. During testing participants were asked to recall the words when given the corresponding pictures (word form test), and recall the definitions when given the corresponding word name (semantics test). The interference consisted of a similar learning task and was presented at different times respect to the end of the first session (5m, 30m, 4h, 24h). Results show that only the word form memory was affected by the interference, while the semantic memory was immune to the treatment. The interference was found to be time limited, supporting the proposal that memory consolidation is the process being affected. Our results suggest a dissociation between the memory systems involved in novel word learning. Semantic aspect would be rapidly incorporated by fast mapping, while the word form memory would form gradually and imply a systems consolidation process.

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Poster

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Title: Impaired sensorimotor integration in auditory feedback control of vocal pitch in Alzheimer's disease

Authors: *K. RANASINGHE[1], N. S. KORT[1], A. J. BEAGLE[1], H. KOTHARE[1], J. S. GILL[1], D. MIZUIRI[1], S. M. HONMA[1], B. L. MILLER[1], K. A. VOSSEL[1,2], J. F. HOUDE[1], S. S. NAGARAJAN[1];
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Abstract: Speech and language networks are affected early in the disease course of Alzheimer's disease (AD). Identifying the neural defects underlying these behavioral deficits will enable us to uncover the earliest manifestations of network dysfunction in AD, and hence useful biomarkers of the disease. A compelling example of speech-motor integration is the pitch perturbation reflex in which speakers respond rapidly to shifts of the pitch of their auditory feedback. In response to brief perturbations of pitch in their auditory feedback subjects alter their vocalization to oppose the direction of the applied pitch shift. Previous neurophysiological studies have linked these specific adjustments in vocal output to integration between sensory feedback error-detection and motor error-correction circuits of speech motor control system. These network integrations are indeed highly vulnerable targets in AD, which is characterized by neuronal loss and functional dysconnectivity of temporal and parietal cortices of the brain. In this study we tested the hypothesis that AD patients will demonstrate altered speech execution ability, specifically the pitch-perturbation reflex, resulting from lack of modulation of distinct network components. We examined the neural and behavioral responses of pitch-perturbation reflex in AD patients (n=12) compared to an age-matched control group (n=11). Subjects phonated the vowel /a/ while a real-time signal processor briefly perturbed (±100 Cent for 400 ms) pitch of their auditory feedback. We used magnetoencephalography and examined the high-gamma (65 - 150 Hz) evoked response during the pitch altered feedback response. We documented the degree of compensation demonstrated behaviorally by each subject by changing their pitch in response to the pitch altered feedback. Behaviorally, AD patients demonstrated an elevated compensatory response compared to age-matched controls (33.4% and 23.0% in patients and controls respectively, $p < 0.0001$, unpaired t test). Neural analysis revealed that, AD patients show a significantly enhanced high-gamma evoked activity compared to age-matched control subjects. Specifically, patients demonstrated an enhanced activity over the left premotor and posterior temporal regions.

Interestingly, this was also accompanied with a significant reduction of prefrontal activity during the early phase of the response. These results implicate the lack of sensory-motor network modulation of speech-motor-control network in AD during auditory feedback control of pitch.

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Poster

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A121996

Title: Graphical features of the structural connectome of the human brain in speech skills

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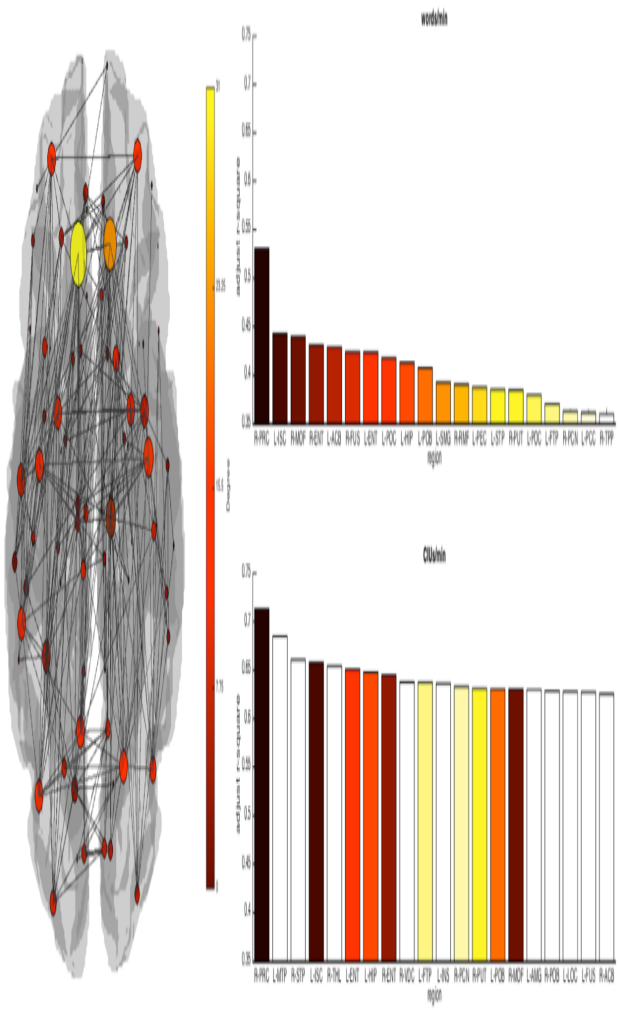
Abstract: The purpose of this study was to find relations between speech skills and structural connectome features. Fifty-four healthy right-handed participants (27 males, 27 females; mean age, 44.02±17.98 year; range, 23-77 year) underwent tests for speech skills that consists of speech fluencies (verbal, semantic, phonemic test), the number of words per minute, the number of correct information units (CIU) per minute, CIU-words ratio, Boston naming test, and Montreal cognitive assessment. And diffusion-weighted images for diffusion tensor imaging (DTI) and T1-weighted image were obtained. Preprocessing was conducted by FSL for DTI fibre tracking and Freesurfer for cortical parcellation and deep grey matter segmentation. To measure edges of a structural connectome, fibre tracking was performed by DSI studio. The parcelled and segmented regions were analysed as nodes. Undirected weighted connectivity between nodes were computed by counting the number of tracked fibres for each node. Connectome features were acquired by using brain network toolbox in Matlab. To find relations between speech skills and connectome features, multiple linear regressions were performed. In addition, significant

regions were sorted and selected by descending order of adjust r-square values of the multiple regression analyses. There were different descending orders for verbal, semantic, and phonemic fluencies. The number of words and CIUs per minute had similar descending order. They contained right precentral gyrus, right entorhinal cortex, left isthmus of cingulate gyrus and left hippocampus. On the other hand, there were also different regions such as left postcentral gyrus and left accumbens for the number of words per minute and left middle temporal gyrus and left frontal pole for the number of CIUs per minute. In summary, structural human connectome can show differences between different speech skills by using graphical features of the connectome. In addition, the connectome features can provide information to reveal characteristics of nodes that are related with speech language.



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Poster

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Title: Left inferior parietal lobe engagement during rule learning from speech involves temporal orienting of attention

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Abstract: Predicting the order of elements in time is an essential capacity that the cognitive system is able to apply to multiple perceptual modalities. In the auditory domain, learning rules from a new language requires keeping track of systematic dependencies while ignoring variable information (e.g. he plays, he sleeps, he speaks). This process may benefit from the use of temporal orienting of attention to the dependent elements as well as executive control in order to ignore irrelevant information. In order to test the involvement of temporal orienting of attention in rule learning we performed a two session experiment (fMRI + rTMS). In the first fMRI session participants were exposed to an artificial language with non-adjacent dependencies in order to localize the peak activation for the task within the left inferior parietal lobe (L IPL). In the second session participants underwent a 1Hz off-line TMS protocol (15 minutes) where the individual peak of activation in the L IPL was stimulated. As a control condition, participants were stimulated in a region of no interest (ROnI: i.e. POz location). Immediately after rTMS application participants performed a temporal orienting task and a language-learning task with a different artificial language compared to that used in the fMRI session. Results showed that stimulation of the L IPL coordinate interfered with temporal orienting of attention, compared to the control coordinate. In contrast, rule learning was enhanced by L IPL stimulation compared to the ROnI. These results indicate that interfering with L IPL activation suppresses orienting of

attention while producing benefits on rule learning. We conclude that, although attention seems to be involved in rule learning, it is not essential and therefore distinct mechanisms may be applied for rule extraction from language under different circumstances.

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Support: NIH R01 EY012440

Title: Superior verbal skills in the congenitally blind

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Abstract: Previous research on the consequences of blindness has provided evidence that congenital absence of sight results in superior verbal memory abilities, possibly as a compensatory mechanism for visual deprivation (e.g., Amedi et al., 2003; Raz et al., 2007). The present study sought to establish whether the superiority of the blind is limited to verbal memory, or whether it generalizes to other verbal tasks or across different kinds of memory abilities. Eight congenitally blind and eight age-matched sighted participants were administered a battery of tests assessing linguistic functions: verbal memory (recall of word lists at different time points after presentation); phonemic and semantic fluency (time-limited generation of items either starting with a specified letter or belonging to a specified category); verbal working memory (backward repetition of number sequences of varying length); and comprehension of sentences varying in syntactic complexity. They were also tested on spatial skills: spatial memory (recall of haptically learned configurations) and spatial imagery (mental construction and comparison of patterns cued verbally by number sequences within a matrix). The congenitally blind group significantly outperformed the sighted controls on most linguistic tests: verbal memory, phonemic and semantic fluency, and verbal working memory. In contrast to the differences on verbal tasks, the two groups were comparable on spatial tasks. Taken together, these results show that congenital blindness is associated with superior verbal skills, including verbal memory and working memory, but that this superiority does not generalize to spatial skills.

Disclosures: **V. Occelli:** None. **S. Lacey:** None. **C. Stephens:** None. **K. Sathian:** None.

Poster

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Topic: F.01. Human Cognition and Behavior

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Title: Which language should I use?: Bilingual speakers show distinct patterns of parasympathetic regulation when code-switching in an emotional context

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Abstract: For many years, researchers have attempted to understand bilinguals' physiological responses to emotional stimuli. Most studies ask participants to listen to, read, or repeat a few words at a time. Although physiological differences are often found, we do not know how physiology might change when emotional events are discussed in detail. Respiratory Sinus Arrhythmia (RSA) is a cardiac measure of parasympathetic function used to index peripheral nervous system (PNS) activation. The aim of this study was to assess whether bilinguals' RSA reactivity during an interview about emotional films would differ depending on the language spoken. 98 Spanish-English bilinguals (M = 20.8 years; SD = 2.11; 73 women) took part in this study, which employed a 2 (emotion: sadness, fear; within-person) X 2 (language frame: Spanish, English; within-person) X 2 (video type: mild emotional intensity, moderate intensity; between-person) mixed experimental design. Each person saw four films and was interviewed (in Spanish or English) about them afterward. Order of language was counterbalanced across participants, but emotion film order was consistent across the Spanish and English blocks (e.g., Sad-Fear-Sad-Fear). Electrocardiograph data was collected for the entire session to derive RSA. We conducted a MANOVA to examine the effects of the first language spoken, the first emotion elicited, and the emotional intensity of the films on RSA reactivity during the four interview phases. There was a significant multivariate effect for RSA reactivity based on the first language used, $F(4, 75) = 5.776$, $p < .001$, and a 2-way interaction of language and intensity $F(4, 75) = 2.655$, $p = .039$. There were marginal univariate effects of language on RSA reactivity to the Spanish interview about sadness, $F(1, 78) = 2.233$, $p = .066$, and to the Spanish interview about

fear, F(1, 78) = 1.769, p =. 075, such that speaking English first resulted in more RSA augmentation. The interaction of language and intensity predicted RSA reactivity for the English interview about sadness, F(1, 78) = 2.282, p = .033, such that starting in Spanish resulted in more augmentation for people who saw mildly intense films, whereas starting in English resulted in more augmentation for people who saw moderately intense films. Our results suggest that when bilinguals code-switch when discussing emotional events, the language they speak first influences PNS activity. Greater RSA augmentation is not necessarily adaptive when interacting with someone else, suggesting that starting a conversation about an emotional event in English hindered participants' ability to effectively regulate arousal.

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Poster

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Topic: F.01. Human Cognition and Behavior

Title: Stimulus expectancy and response entropy in adult cochlear implant users

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Abstract: Cochlear implants (CI) have recently gained traction for older adults whose hearing loss is too severe to receive significant benefit from hearing aid use. Indeed, post-lingually deafened older adults are receiving implants well into their 80s. Despite the increase in CI use by older adults, there is a lack of research into the issues facing this emerging population at the level of natural discourse. Almost the entirety of research on CI users has been on intelligibility with single word or simple sentences. Faced with perceptual challenges (e.g., speech is often under-articulated and is rapid, often exceeding 180 wpm) and declines in working memory that accompany aging, one might expect older CI users to require more phonetic information from a word to identify it in the absence of a constraining context than younger CI users. Moreover, this difference could be reduced or eliminated in the presence of a constraining context. In addition, one might expect that response entropy, calculated as the number of potential competitors and the uniformity of their probability distributions, may affect the onset duration needed to correctly identify a target word. We report the results of an experiment in which younger and older adult CI users listened to sentences with progressive increases in contextual constraints from a no

context condition to a high context condition. Sentence final words were presented using a word-onset gating paradigm, in which words were heard with increasing amounts of word-onset information until they were correctly identified. Results will be discussed in terms of the effects of linguistic context (target expectancy) and response entropy (competition from the distribution of lexical alternatives that may also fit the context) on word recognition.

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Title: The development of parsing routes for complex words in second language learners

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Abstract: While learning a second language, proficiency and abilities in that language continuously develop. Active knowledge of semantics and grammar increases, along with automatised skills needed for grammatical processing. These skills are particularly necessary as many words in everyday language are complex, i.e. they consist of more than one meaningful element (=morpheme), e.g., cat-s, cat+plural marker (inflection). Previous studies show the ability of native (L1) speakers to parse novel complex words (derivations, e.g., chicken+ish) online even if they have never encountered them previously. How do second language (L2) learners process complex and novel derivations in their L2? To address this issue, a passive multifeature MMN paradigm was used while recording EEG. During the experiment, L1

speakers as well as beginning and advanced learners of Finnish were presented with spoken 1) real derived words, 2) novel derivations (novel combinations of a real stem+real suffix), and 3) pseudowords (real stem+pseudosuffix). In L1 speakers, real derivations elicited a larger MMN than novel derivations, demonstrating early automatic access of full-form memory traces for real derivations. In contrast, pseudowords showed larger responses than both novel and existing derivations, demonstrating a syntactic ERP pattern. Compared to L1 speakers, advanced L2 learners also showed a syntactic ERP pattern for pseudowords but only when compared to real derivations. In advanced L2 learners, no differences were found between real and novel derivations, pointing towards weaker memory traces for real derivations as compared to L1 speakers. Finally, no significant differences were found between the stimuli types in beginning learners. We conclude that L1 speakers have stronger memory traces for derived words and parse and integrate novel meaningful derivations more flexibly than L2 learners. Advanced L2 learners, however, have developed sensitivity to lexicality as well as to the morphosyntactic structure of complex words, while beginning learners have not, as suggested by the syntactic ERP pattern. Instead, beginners do not distinguish between these different morphology types yet and therefore possibly use the parsing route to decompose all complex items into their constituents.

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Support: NIH-NINDS P50 NS22343

Title: Non-verbal communication during the speaking and listening phases of a dyadic conversation in children with high functioning autism and children with williams syndrome

Authors: ***M. B. KIM**[1], P. LAI[2], D. TRAUNER[3], J. REILLY[4], U. BELLUGI[2];
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Abstract: How do children with different neurodevelopmental disorders use non-verbal communication when communicating with an adult compared to typically developing children?

In this study, school age children (ages 7-14) were examined during a dyadic social interaction with an adult. Typically developing (TD) children (n = 26), children with High Functioning Autism (HFA; n = 23) and children with Williams Syndrome (WS; n = 14) were observed in their non-verbal communicative behaviors, focusing on eye gaze, facial expression, and their co-occurrences. We examined these behaviors during both the speaking and listening portions of the interview. According to the results, there was no significant difference between the duration of speaking segments ($p = 0.258$) and listening segments ($p = 0.132$) for all three groups. Next, the percentage of eye contact was examined during speaking portions and all groups behaved comparably ($p = 0.800$). However, during the listening phase, the percentage of eye contact was significantly different between the HFA and WS groups, and between the HFA and TD groups. In both cases, the HFA group produced a smaller percentage of eye contact compared to their peers. For the production of facial expression during the speaking phase, a significant difference was observed ($p = 0.032$). Post-hoc testing using Tukey-HSD found a difference between the HFA and WS groups; HFA group was less expressive as the WS group. A trend was found for the HFA and TD comparison ($p = 0.072$), once again the HFA group were producing less facial expression during the speaking phase than the TD group. The percentage of facial expression during the listening phase was significantly different ($p < 0.001$) among the three groups. The HFA group did not use facial expressions as frequently as the WS and TD groups. Finally, co-occurrences of eye contact and facial expression during the speaking phase was not significantly different ($p = 0.114$) in our groups. Importantly, co-occurrences of eye contact and facial expression during the listening phase did result in group differences ($p < 0.001$) as the HFA group had a significantly lower percentage of co-occurrences than both the WS and TD groups. Our results suggest that the HFA group behave similarly during both the listening and speaking portions, a pattern not observed in the TD and WS groups. For the TD and WS groups, our results suggest nonverbal behaviors are more expressive during the listening phase than the speaking phase, especially eye contact. To answer our initial question, the HFA group showed a pattern of hypo-social communicative behaviors compared to the WS group, which displayed non-verbal behaviors similar to the TD group during this task.

Disclosures: **M.B. Kim:** None. **P. Lai:** None. **D. Trauner:** None. **J. Reilly:** None. **U. Bellugi:** None.

Poster

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Support: NIH NICHD 2P01 HD 33113-14

Title: Characterizing multiple channels of social behaviors and expressivity in adults with Williams Syndrome during narratives

Authors: *T. V. DANG[1], P. LAI[1,2,3], J. REILLY[3], U. BELLUGI[1];
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Abstract: Williams Syndrome (WS) is a genetic disorder, characterized by hyper-sociability and gregariousness. Previous studies using a wordless picture book, Frog, Where Are You? (Mayer, 1969) found school aged children (5-10 years) with WS had high levels of affect and sociability in their narratives (Losh et al., 2000). How are affect and sociability expressed in adults with WS? The goal of this study is to better define the social phenotype of adults with WS by analyzing multiple channels of communication in social and expressive behaviors. In this study, participants (WS n=22, TD n=16) were asked to produce narratives as we examined: 1) evaluative devices, 2) eye gaze behaviors, 3) hand gestures. Using the Reilly Evaluation Coding System (Reilly et al.,1998; 2004), there were no differences in total evaluations, which included cognitive and social elements. When we examined social categories (i.e., sound effects, attributing emotions, intensifiers, etc.), a significant difference was found (p= 0.007); the WS group used 62% of social evaluations, while the TD group used only 47%. For example, 18 of the 22 WS individuals had at least one sound effect in their narratives, while only 3 of the 16 TD individuals produced a sound effect in their narratives. When investigating eye gaze behaviors, there were significant differences in average frequency (p=0.011) and average duration (p=0.003); the WS group produced more eye contact. The last expressive channel analyzed was the use of gestures. Interestingly, only 38% of the TD group produced one gesture during the narrative task, while over 72% of the WS group produced gestures. A Chi-Square test found a dependent relationship between group and gesture use χ;2(1,37)=4.259, p=0.039. Our results suggest that in these three channels, social behavior and expressivity in the WS group were more evident compared to their TD peers. In line with the results from children with WS (Losh et al., 2000; Reilly et al., 2004), adults with WS are producing more social evaluative devices, which are used to attract and maintain the listener's attention through the narrator's perspective and attitude. The eye gaze results are noteworthy since this task does not require explicit eye contact with the experimenter, yet the WS group still uphold eye contact suggesting their predisposition to engage with others. The gestures observed highlight the expressivity of the WS group, as the majority of the gestures were used to emphasize their stories, a pattern not observed in the TD group. Taken together, these results can better help define the adult WS social profile, and future research can begin linking social behaviors to potential neural mechanisms.

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Topic: F.01. Human Cognition and Behavior

Support: Doris Duke Foundation 2012062

NIH/NCATS KL2TR000102

Title: Task-based connectivity between the inferior frontal lobes increases following left hemisphere stroke and is associated with worse naming performance

Authors: *L. SKIPPER-KALLAL[1], E. H. LACEY[1,2], S. XING[1], K. SPIEGEL[1], M. E. FAMA[1], P. E. TURKELTAUB[1,2];
[1]Neurol., Georgetown Univ., Washington, DC; [2]MedStar Natl. Rehabil. Hosp., Washington, DC

Abstract: The role of the right hemisphere in aphasia recovery has been debated for over a century. Some argue that the right hemisphere plays a compensatory role, aiding recovery (e.g., Basso et al., 1989), while others posit that right hemisphere activity interferes with recovery (e.g., Barwood et al., 2011). In this experiment, we examined the functional networks that synchronize during covert object naming, and how the communication within this network relates to naming performance outside of the scanner, controlling for differences in stroke distribution that also relate to performance. Twenty participants with chronic left hemisphere stoke, as well as 25 age-matched controls, participated in this study. The participants underwent a T2* weighted MRI scan while they performed a delayed-response object naming task. Only correct trials were analyzed. Participants also underwent a battery of language and other cognitive tests, which were reduced to four oblique factors (Naming, Motor speech, Executive function and Comprehension) using factor analysis. VLSM analyses were carried out for the Naming factor. Lesions in the left pars triangularis and pars orbitalis were associated with worse performance on Naming. To account for relationships between lesion location and naming ability, we calculated the proportion of the VLSM results damaged in each individual (Percentage of Critical Area Damaged, PCAD). The functional data was then analyzed using a psychophysiological interaction (PPI) analysis, which identified regions that synchronized with right BA 44 specifically during word retrieval. Participants in the stroke group showed greater connectivity than controls between the seed region and left pars triangularis and insula during word retrieval. A regression was then carried out examining how activation in this left hemisphere region related to Naming performance, while controlling for age, gender, education,

handedness, chronicity, lesion size and PCAD, in the stroke group. The level of activation in the area identified by the PPI analysis significantly predicted participant performance on the Naming factor, such that high levels of activation related to worse performance. Activation of this region during word retrieval also had a significant negative relationship with performance on the Philadelphia Naming Test. These results show that the right frontal lobe synchronizes with left frontal language areas to a greater degree for stroke participants than for healthy people, and activation of this region in the left hemisphere during a language task is related to poor naming performance, even when controlling for the impact of the stroke itself.

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Title: Predicting behavioral preferences in language use from electrophysiological activity

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Abstract: Traditional event-related potential (ERP) research has often divided components into "stimulus-locked" and "response-locked". Yet, when we consider that ERP components index evoked electrical activity within the perception-action loop, it becomes clear that a component is not "response-locked" but rather "response-locking". Response-related ERPs have been observed in a range of response settings (e.g. the readiness potential and the P300 for positive or neutral settings, the ERN for negative or incorrect responses). In studies on language, this has been extensively studied with a late positivity for dispreferred sentences, which seems to be strongly dependent on the task (Haupt et al 2008). Additionally, neural correlates for behavioral preferences without a canonical intersubject answer have been observed in other domains (e.g. beverage: McClure et al 2004, car manufacturer: Schaefer et al 2006), suggesting that it may be possible to measure preferences in language. (An example of such preferences is the pronunciation of "route" in American English -- it can rhyme with either "root" or "gout" depending on the individual speaker.) Here, we demonstrate the feasibility of using the electrophysiological response to predict binary judgments in language, thus deriving action from

brain activity. Moreover, we show that this works in both judgments with and without a canonical answer. Data were reanalyzed from Roehm et al (2013). Sentences were presented phrase-wise using RSVP to 32 monolingually raised native speakers of German (17 women, mean age 24) after they had given informed consent. After each sentence, subjects performed a binary acceptability judgment as well as a probe task. In 3 conditions, the acceptability judgment had a canonical answer, while the fourth lacked one and was subject to individual preference. Using generalized linear mixed-effects models with the single-trial acceptability judgment as the dependent variable, we found that the mean single-trial EEG amplitude from centro-parietal sites in the 600-800ms post-stimulus time window was a significant predictor of response across all conditions. Restricting the analysis to the condition without a canonical judgment reduced the size of the effect but did not remove it. These results demonstrate the feasibility of using electrophysiological activity to predict behavior, thus situating action in its correct place in the perception-action loop. Moreover, they suggest that the difference between "preferred" and "required" response is a quantitative and not a qualitative one.

Disclosures: **P.M. Alday:** None. **D. Roehm:** None. **M. Schlesewsky:** None. **I. Bornkessel-Schlesewsky:** None.

Poster

619. Language III

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Topic: F.01. Human Cognition and Behavior

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McDonnell Center for Systems Neuroscience

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Title: Cognitive demands in speech comprehension task modulates the effective connectivity: An optical tomography study

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Abstract: Speech perception is processed in a hierarchical and distributed fashion. Although neuroanatomy of speech perception is thoroughly investigated, little is known about how these distributed regions interact during the course of speech comprehension. In these study we use a semi-exploratory approach and investigate interregional interactions within speech network. Using event-related high-density diffuse optical tomography (HD-DOT) recordings of the brain hemodynamic activity during processing of auditory sentences that vary in their intelligibility and linguistic complexity, we assessed the modulatory effect of task demands on interregional interactions. Quiet imaging setting of HD-DOT system enables presenting the auditory stimulus in an acoustically well controlled environment and therefore isolating the complexity to linguistic aspects of speech. We presented listeners with spoken sentences that contained either a subject-relative (syntactically easy) or object-relative (syntactically complex) center embedded clauses, along with a control noise condition. In order to identify which networks have connectivity values that are modulated by task demands, we employed generalized psycho-physiological interaction (gPPI) analysis method. We modeled and characterized the activity in a brain region in terms of the interactions of both a task and functional connectivity to another region. Results show that intelligibility significantly increases the effective connectivity (EC) between left frontal lobe and several cortical areas also modulates the connections between left angular gyrus and left middle frontal gyrus in several regions. Processing complex sentences increases bilateral connections between ventral parts of prefrontal cortex and has strong modulatory effect on the connections between left temporal cortex and right ventral inferior frontal gyrus as well as connections between left parietal lobe and left prefrontal cortex. Overall, results highlight the presence of a hierarchical EC within distributed speech processing network.

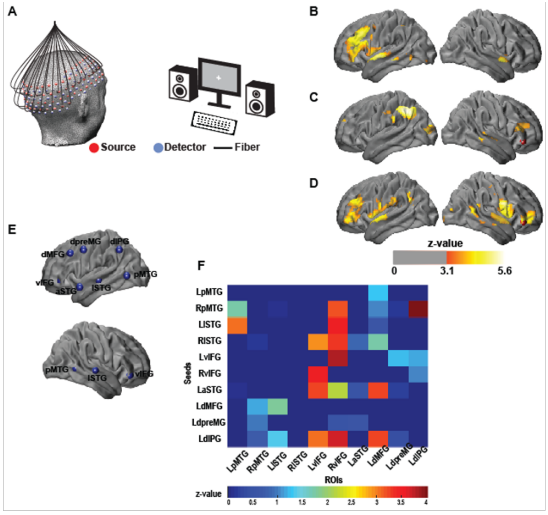

Figure 1: (A) Schematic view of HD-DOT experimental set up, subject position and imaging cap structure (a subset of optical fibers is shown for clarity). (B) Mani effect of sentences (Complex sentences > Noise), (C) Resting state functional connectivity for seed at right ventral inferior frontal gyrus (RvIFG). (D) Effective connectivity between RvIFG seed and rest of brain increases during complex sentences compared to noise. (E) Canonical/group seeds. Seeds at 10 ROIs located at posterior middle temporal gyrus (pMTG), lateral superior temporal gyrus (lSTG), ventral inferior frontal gyrus (vIFG), anterior superior temporal gyrus (aSTG), dorsal middle frontal gyrus (dMFG), dorsal premotor gyrus (dpreMG) and dorsal inferior parietal gyrus (dIPG) were selected for effective connectivity analysis. (C) Effective connectivity shows effective between several seeds with and right and left vIFG connectivity increases significantly during complex sentence processing.

Disclosures: M.S. Hassanpour: None. **A.T. Eggebrecht:** None. **J.E. Peelle:** None. **J.P. Culver:** None.

Poster

619. Language III

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 619.21/W27

Topic: F.01. Human Cognition and Behavior

Title: Using cochlear implant simulations to examine the effects of signal degradation and linguistic complexity on sentence comprehension and listening effort

Authors: *E. ATAGI[1], N. M. AMICHETTI[1], W. ALFORD[1], Y.-Y. KONG[2], A. WINGFIELD[1]; [1]Volen Natl. Ctr. for Complex Systems, Brandeis Univ., Waltham, MA; [2]Communication Sci. and Disorders, Northeastern Univ., Boston, MA

Abstract: Use of cochlear implants among older adults is increasing. Currently, users' degree of success with their cochlear implants is nearly always measured by their ability to understand speech consisting of single words or simple sentences. Spoken communication, however, generally consists of a series of more complex sentences that require greater processing demands. Such processing demands cause older adults with hearing loss to show poor

comprehension of spoken sentences with complex syntax, even when they are able to identify the words (Tun et al., 2010). This challenge arises due to the extra effort required in the early perceptual stages of speech processing, which in turn negatively affects the later stages of comprehension and encoding (e.g., Rabbitt, 1991). Thus, when combined with age-typical slowing of processing speed and limits to attentional capacity, linguistic complexity can compound the effects of even a mild hearing loss in older adults (Wingfield et al., 2006). The extra effort required for successful identification of a degraded signal has been recently demonstrated with young adults listening to cochlear implant simulations (i.e., spectrally degraded, vocoded speech). These studies observed gradient levels of listening effort with increasing spectral resolution even beyond the point at which speech intelligibility plateaued at a high level (Pals et al., 2013; Winn et al., 2015). The present study used vocoded speech at three levels of spectral resolution to simulate cochlear implant listening in older and young adults to examine the effort necessary to process speech with multiple degrees of both signal degradation and linguistic complexity. Listeners were presented with syntactically complex sentences at two levels of difficulty: an easier, subject relative construction (e.g., The boy that kicked the girl left the room) and a harder, object relative construction (e.g., The boy that the girl kicked left the room). Comprehension was measured by the accuracy of listeners' responses to a comprehension question following each sentence (e.g., Who did the kicking? Who was kicked?). Additionally, listening effort was measured by recording listeners' pupil sizes before, during, and after each sentence presentation. Results were analyzed for response accuracy to the comprehension questions and the listening effort differentially incurred by the different levels of signal degradation and linguistic complexity.

Disclosures: **E. Atagi:** None. **N.M. Amichetti:** None. **W. Alford:** None. **Y. Kong:** None. **A. Wingfield:** None.

Poster

619. Language III

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Topic: F.01. Human Cognition and Behavior

Support: ERC Grant 209656

Title: The impact of stress on precise and rough speech processing in early infancy

Authors: *C. TEICKNER[1], A. BECKER[2], U. SCHILD[1], C. K. FRIEDRICH[1];
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Abstract: We formerly showed that when it comes to speech processing infants seem to process phonemes and prosody separately (Becker et al., 2014). In the current study we investigated how detailed phonetic processing (place of articulation) is when stress in the prime-target pairs either matches or mismatches. We presented 3-month-old infants with primes (single syllables) and targets (complete early learned initially stressed German words) while recording their event-related potentials (ERPs). Three types of phoneme overlap were presented in prime-target pairs: complete overlap (e.g., ma-Mama), partial overlap (e.g., na-Mama) or non-overlap (vo-Mama). These three conditions were presented two times, once with stressed primes and once with unstressed primes. In accordance with the results of a previous study solely on phoneme processing (Teickner et al., 2014), we found that at three months after birth speech processing is precise enough to even track variation of the place of articulation of only one phoneme. Our results show that even when primes are unstressed, infants still perceive slightest phoneme mismatches (e.g., na - Mama). Previous studies found that two-day-old newborns prefer their native language over a foreign language (e.g., Moon et al., 1993). This means that, already *in utero*, they process prosody that can be applied in speech perception after birth. However, since most of the fine-grained segmental information does not get through the womb, the processing of phonemes can only begin after birth. In the current study, we found that phonemes and prosody are processed separately. It seems that when 3-month-old infants perceive speech, processing of segmental information is given top priority. Thus, seemingly the mechanism responsible for processing suprasegmentals can be suppressed when focusing on phoneme processing becomes more important.

Disclosures: C. Teickner: None. **A. Becker:** None. **U. Schild:** None. **C.K. Friedrich:** None.

Poster

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Topic: F.01. Human Cognition and Behavior

Support: the Natural Science Foundation of China Grant 31300842

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Title: The bilateral inferior parietal lobules in support of Chinese multi-character word recognition

Authors: *N. LIN;
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Abstract: The majority of Chinese words are multi-character words. In Chinese text, single and multi-character words are embedded in long strings and there is no perceptual cue to mark word boundaries. Therefore, a Chinese sentence can be segmented into words as well as nonwords. The lack of perceptual word boundaries does not harm Chinese reading, indicating that Chinese readers can differentiate multi-character words from nonwords highly efficiently. How Chinese readers differentiate multi-character words from nonwords is an important and special question in psychological and computational linguistic sciences and has been investigated for over two decades. However, until now, only one neuroimaging study (Zhan, Yu, & Zhou, 2013) has investigated the neural mechanisms underlying that processing. Using functional MRI, we investigated Chinese multi-character word recognition by comparing brain activations evoked by two-character words (e.g. “奔跑”), transposable nonwords (e.g. “跑奔”), and nontransposable nonwords (e.g. “跑吻”) during lexical decision. We included the transposable nonword condition because a direct comparison between the word and nonword conditions might be confounded by factors associated with response-type and stimulus familiarity. It has been found that a transposable nonword, which is produced by transforming the positions of the characters of a real word, can automatically activate the corresponding word representation. Therefore, the comparison between transposable and nontransposable nonwords should to some extent reveal the neural mechanisms underlying multi-character word recognition. We found that the transposable nonwords evoked stronger activations in the bilateral inferior parietal lobules (bIPLs) than nontransposable nonwords. No other brain activation difference between transposable and nontransposable nonwords was observed. The involvement of the bIPLs in Chinese multi-character word recognition was further confirmed by a conjunction analysis of the contrasts “word > nontransposable nonword” and “transposable nonword > nontransposable nonword”. In addition, we found that the bIPLs showed stronger activation to high-frequency words than to low-frequency words. Our results are in accordance with a recent finding that the activation level of the bIPLs during Chinese reading is a significant biomarker for one’s knowledge of written Chinese. In terms of the existing evidence about the functions of the bIPLs in language processing, our findings indicate that Chinese multi-character word recognition might rely on the access of the mapping between orthographical and phonological/semantic representations.

Disclosures: **N. Lin:** None.

Poster

619. Language III

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 619.24/W30

Topic: F.01. Human Cognition and Behavior

Title: The effect of degree of automaticity in processing hierarchical structure in arithmetic and language

Authors: *H.-A. JEON, A. D. FRIEDERICI;
Max Planck Inst. for Human Cognitive and Brain Sci., Leipzig, Germany

Abstract: It has recently been suggested that a degree of automaticity in cognitive processing is a crucial factor in modulating the functional organization of the prefrontal cortex (PFC): the posterior-to-anterior gradient system for more controlled processes with a low degree of automaticity and the posterior-confined system for automatic processes with a high degree of automaticity. The neural mechanism involved in processing arithmetic has been investigated along with mathematical proficiency. It has been suggested that people with high proficiency retrieve mathematical facts stored in memory quickly and effortlessly, whereas people with low proficiency derive answers from procedural knowledge that is slow and prone to error. Taking these observations together, we investigated the neural networks for hierarchical processing in language and arithmetic depending on individual levels of proficiency. We recruited two groups of participants: mathematicians with a high level of mathematical proficiency and non-mathematicians with a low level of mathematical proficiency. Participants went through hierarchical processing with center-embedded sentences in language and center-embedded calculations in arithmetic. Using functional magnetic resonance imaging, we observed a significant difference between groups when processing arithmetic. While a broad fronto-parietal network was being activated in non-mathematicians, focal activation in the left precentral gyrus and left superior parietal lobule were found in mathematicians. However, no group difference was found in language. To elucidate the effect of degree of automaticity on the functional segregation within the PFC, a correlation analysis was conducted between individual degree of automaticity and the percent BOLD signal change from peak activations within the PFC. As a result, significant activation in its posterior area (precentral gyrus) was observed for arithmetic in mathematicians, being positively correlated with the degree of automaticity. However, non-mathematicians recruited a wide posterior-to-anterior network, with peak activation in the anterior region (pars triangularis, BA45) showing a negative correlation with the degree of automaticity. For language, no group difference was found in the activation pattern within the

PFC and the posterior region of the PFC (BA44) was positively correlated with the degree of automaticity in both groups. From the current data we discovered that the organizational principle of the degree of automaticity in the PFC can also be applied to the arithmetic domain, making a possible broad generalization of this organizational rule.

Disclosures: H. Jeon: None. **A.D. Friederici:** None.

Poster

619. Language III

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Topic: F.01. Human Cognition and Behavior

Support: CAPES

HCFMUSP

Title: Phonological verbal fluency task demands more attentional resources than Semantic verbal fluency task in patients with Parkinson's disease

Authors: *M. E. PIEMONTE, M. R. PIKEL;
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Abstract: The reduction in dopamine levels in striate cortical circuits caused by Parkinson 's disease compromises the gait automatic control by progressively limiting the ability to manage multi-tasks. However, it remains unclear what the more efficient way to test gait performance in dual-task avoiding the influence of the learning and educational level.Aim: To compare the efficacy of two different forms of the verbal fluency task used as a secondary task in order to promote the division of attention during the gait in PD patients.Methods: Gait performance of the 30 idiopathic PD patients, mean age of 64.5 years, mean years of schooling 4-12 , at stages 1-3 of according to the Hoehn&Yahr Classification, asymptomatic for depression and dementia, were tested 4 times in 2 weeks. The first two tests were performed on the same day, with 2 hours of rest between them. The other two tests were performed 7 and 14 days after the first day. The participants were asked to walk for 30 seconds in a comfortable speed in three different conditions: Single Task (ST), i.e., without a secondary task; Dual-Task condition with phonological form of verbal fluency task (DTP), in which the subjects are required to produce words, as many as possible, beginning with a given letter (F-A-S); and Dual-Task condition with semantic form of verbal fluency task (DTS), in which subjects are asked to articulate words, as

many as possible, belonging to a given category as fruits, vegetables and animals.Results: One 3X4 RM-ANOVA using as factor Condition (ST, DTP, DTS) and test time points (T1,T2,T3,T4) as repeated measures for gait speed showed a significant effect only for conditions (p=.00001,ES=.99). Tukey pos hoc test showed significant differences in speed between ST and DTP conditions (p=.0001,ES=.99), and ST and DTS (p=.0001,ES=.99). One 2X4 RM-ANOVA using as factor Conditions (DTP and DTS) and test time points (T1,T2,T3,T4) for gait speed and number of words evoked showed only a significant effect of conditions (p=.01,ES=.71 and p=.00002,ES=.99 respectively). Tukey pos hoc test showed a significant lower speed in the DTP and significant higher number of words in the DTS condition. There was no significant correlation between gait speed and number of words evoked and years of schooling. Conclusion(s): Both forms of verbal fluency task were efficient to promote a decrease in gait performance, which is expected under dual-task conditions, and, more importantly, neither one suffered learning or educational level effect. The DTP test demanded more division of attention. It can be observed by more reduction in gait speed and less number of words evoked in comparison with DTS.

Disclosures: **M.E. Piemonte:** None. **M.R. Pikel:** None.

Poster

619. Language III

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Title: A functional anatomical map of human speech production

Authors: ***K. KATLOWITZ**[1], M. A. LONG[2], M. SVIRSKY[3], T. MCALLISTER BYUN[4], R. C. CLARY[2], H. OYA[5], M. A. HOWARD, III[5], J. D. W. GREENLEE[5];
[2]Dept. of Neurosci. and Physiol., [3]Dept. of Otolaryngology, [4]Dept. of Communicative Sci. and Disorders, [1]New York Univ. Sch. of Med., New York, NY; [5]Human Brain Res. Lab, Dept. of Neurosurg., Univ. of Iowa, Iowa City, IA

Abstract: Spoken language is one of the fundamental ways that we interact as a society. Two important neocortical centers that have been most commonly studied with respect to speech production are a subregion of the inferior frontal gyrus (commonly referred to as Broca's area) and the ventral primary motor cortex. Activity within both of these areas is correlated with a number of speaking tasks, as measured by fMRI (Price, 2012) or electrocorticography (Bouchard et al., 2013; Sahin et al. 2009; Cogan et al. 2014). Focal perturbations to these circuits such as electrical stimulation (Penfield and Roberts 1959; Ojemann 2002) and transcranial magnetic stimulation (Pascual-Leone et al. 1991) can result in speech arrest, suggesting that these regions are likely to be involved in speech production. However, the relative roles undertaken by Broca's area and the precentral gyrus in the production of speech are still poorly understood. To address this issue, we used a device to rapidly and reversibly lower the temperature of focal motor and premotor cortical areas in neurosurgical patients, controlling the speed of neural dynamics within those regions in an analog manner (Bakken et al., 2003; Long and Fee, 2008; Tang et al., 2010). By analyzing the changes to the fine structure of speech resulting from this manipulation, we could establish a causal relationship between those local circuits and speech production. We cooled 42 total areas in 16 awake individuals undergoing a craniotomy (1-7 regions per patient) while they recited two alternating word lists ('Monday', 'Tuesday', 'Wednesday', 'Thursday', 'Friday' or '21', '22', '23', '24', '25'). Speech timing was measured by manually demarcating reproducible spectrotemporal landmarks that often corresponded to identified phonemes. Changes in speech 'quality' were measured on a visual analog scale using a crowdsourcing approach. Mapping the effect to the cooling location revealed that cooling the left hemisphere resulted in significant speech changes in 14 of 30 cases while the same manipulation performed on the right hemisphere was only effective in 1 out of 12 instances. Strikingly, the timing and quality of human speech can be manipulated preferentially in specific brain regions following left-sided cooling. Cooling in the inferior frontal gyrus resulted in significant changes in speech timing, while cooling in the motor strip resulted in the degradation of speech quality. These results support a segregated, hierarchical model of speech production.

Disclosures: K. Katlowitz: None. **M.A. Long:** None. **M. Svirsky:** None. **T. McAllister Byun:** None. **R.C. Clary:** None. **H. Oya:** None. **M.A. Howard:** None. **J.D.W. Greenlee:** None.

Poster

620. Human Decision Making: Perception, Motor, and Attention

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 620.01/W33

Topic: F.01. Human Cognition and Behavior

Title: A novel implicit associative learning framework: validation, role of attention and relation to Bayesian decision making

Authors: *A. ALAMIA[1], A. CLEEREMANS[2], E. OLIVIER[1], A. ZENON[1];
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Abstract: Implicit learning provides a rare opportunity to investigate how the brain operates in the absence of conscious intent. It has been investigated in many different domains, from sequence to statistical learning and from artificial grammar learning to contextual cueing in visual search. The current study is composed of three parts: first we propose a new experimental design to investigate how simple stimulus-response associations can be learned implicitly; second, we study the relationship between implicit learning and visual attention, and third we aim to determine how implicit and explicit information is combined together when making a perceptual discrimination task. All experiments followed the same procedure and design. In each trial, the participants had to report the motion direction of a patch of dots, which could be of three different colors. Unbeknownst to the participants, two of these colors were always associated with the same direction/response, while the third color was uninformative. In the first part, across a series of four experiments, we showed that the participants learned systematically the association between color and direction, while remaining strikingly unaware of it. In addition, we showed that performance feedback was crucial to the occurrence of implicit learning in this task, and that both the stimulus-response and stimulus-stimulus associations could be implicitly learned. In the second part we tested whether the allocation of visual attention to the informative feature (i.e. color) is required to learn the association and whether regularities, even though learnt implicitly, attract attention. Preliminary results show that attention is indeed required for implicit learning to occur, and that regularities attract attention consistently. Finally, we investigated in a last series of experiment how implicit information is combined with explicit information to make a perceptual decision. Interestingly, preliminary results suggest that, in contrast to our predictions, implicit information has a constant weight in the decision, irrespective of the reliability of explicit information, in violation of Bayesian optimal weighting of information sources. In conclusion, we provide a novel robust implicit learning framework, which allows us to investigate the interaction between implicit learning and other higher cognitive functions, such as visual attention and perceptual decision making.

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Poster

620. Human Decision Making: Perception, Motor, and Attention

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Title: A review of transcranial direct current sensation monitoring

Authors: *M. P. WEISEND[1], M. S. SHERWOOD[1], M. K. HOWES[2], K. M. GRUNDY[2]; [1]Wright State Res. Inst., Beavercreek Township, OH; [2]Antioch Col., Yellow Springs, OH

Abstract: Transcranial direct current stimulation (tDCS) is widely touted as a method to enhance cognition in healthy participants and treat symptoms of conditions such as attention deficit hyperactivity disorder, stroke, depression, tinnitus, and others. tDCS causes sensations at the skin's surface, therefore, proper blinding procedures are critical to determining tDCS effectiveness. At present, the results of blinding procedures are reported infrequently and incompletely. We examined blinding techniques and there quantification in 200 primary research papers from 2011-2015. Nearly all reports claimed single (63%), double (32.5%), or other (6.5%) blinding techniques. However, only 32.5% of papers reported gathered participant input for tDCS elicited sensations and still fewer 10.5% presented the results of sensation questionnaires. Only 3.5% of the papers reported the findings of sensation questionnaires, performed an appropriate statistical analysis, and found effective blinding. One paper reported ineffective blinding with similar rigor. In spite of the common knowledge that tDCS elicited sensations can reveal information about stimulation conditions to subjects and researchers, quantification, reporting, and analysis of tDCS induced sensations to support claims about blinding are rare in the extant literature. The lack of rigorous support for blinding claims in tDCS studies invites well founded skepticism about the validity of tDCS as a technology to enhance cognition in healthy participants and treat neurological disorders. The tDCS community would benefit from an agreed upon standard for reporting results. The standard should include reporting differences in sensations between tDCS conditions to better understand the empirical support for the claims of blinding participants.

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Poster

620. Human Decision Making: Perception, Motor, and Attention

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 620.03/W35

Topic: F.01. Human Cognition and Behavior

Title: Contribution of attentional selection to learning during probabilistic inference

Authors: *C. GUO, S. G. HOFFMAN, P. KHORSAND, A. SOLTANI;
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Abstract: Naturalistic decision making is challenging as it often entails simultaneously learning about and combining partial evidence from various sources of information. Learning is especially challenging when processing multiple sources of information (i.e. cues), because the brain must solve the nontrivial task of assigning the correct weight to each cue using binary feedback (e.g. reward/no reward, success/failure), which is probabilistic in nature. The simultaneous aspect of learning and cue combination, as well as the large number of available cues, point to a role for attentional selection in naturalistic decision making and probabilistic inference. Existing information can influence what cues are attended/processed and can subsequently impact decision making. Moreover, it is possible that only evidence associated with the attended/processed cues is subsequently updated following reward feedback. In order to directly test the influence of attentional selection on probabilistic inference, we manipulated the saliency of 1 of 4 cues used to make decisions. More specifically, on each trial subjects were presented with 4 cues (simple geometric shapes) and asked to choose between two alternative options (red and blue targets) in order to receive reward points. Each cue carried a unique weight of evidence (WOE, log likelihood ratio that the cue is presented given either red or blue target is assigned with reward). The combined WOE from all cues presented on a given trial determined the reward probabilities on the two targets. After completing a few blocks of decision making and receiving feedback (choice session), the subjects estimated how much each cue or a combination of cues predicted reward on one of the two targets (posterior probabilities). We examined how biases in subjects' estimates of posteriors changed when we increased the saliency of one shape (via increasing brightness of the particular shape). We found that attentional manipulation during the choice session did not increase the subjects' tendency to select the choice alternative supported by the highlighted shape. However, this manipulation selectively increased the subjects' estimates of the predictive power of the highlighted shape. In other words, although reward feedback may stop subjects from developing an overall erroneous bias due to increased saliency, its interaction with attentional selection altered what was learned about individual shapes. Overall, these results demonstrate that the interaction between attentional selection and reward processes has a strong influence on probabilistic inference.

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Poster

620. Human Decision Making: Perception, Motor, and Attention

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Support: FRS-FNRS: MIS F.4512.14

Title: Disentangling the involvement of primary motor cortex in value-based reinforcement learning and value-based decision making

Authors: ***G. DEROSIERE**, P. VASSILIADIS, S. DEMARET, A. ZENON, J. DUQUE; Inst. of Neurosci., Brussels, Belgium

Abstract: When one makes the decision to act in the physical world, the neural activity in primary motor cortex (M1) encodes the competition between potential action choices. Traditional approaches have viewed this activity as reflecting the unfolding of the outcome of a decision process taking place upstream. However, a recently emerging theoretical framework posits that the motor neural structures directly contribute to the decision process. We recently tested this hypothesis by using continuous theta burst stimulation (cTBS) to alter activity in M1 while participants performed a task that required them to select between two fingers in the right hand based on the color of a stimulus (green or red, explicit instruction). Importantly, this finger choice was biased such that, to earn more money, the subjects also had to take into account the shape of the stimulus (circle or square, undisclosed manipulation). So the motor response depended, on the one hand, on a perceptual decision process, interpreting the color of the stimulus according to instructed rules and, on the other hand, on a value-based decision process relying on reinforcement learning. Interestingly, cTBS over M1 modified the extent to which the value-based process influenced the subjects' decisions whereas it had no effect on their ability to make a choice based on perceptual evidence. Importantly, in that study, cTBS was applied at the very beginning of the experiment, before the subjects had learned the task. Hence, we cannot tell from that work whether the effect of M1 cTBS was due to an alteration of value-based reinforcement learning or of value-based decision making, which takes place once learning is complete. Here, we present a study in which we intend to use the same task but with cTBS applied at different times in order to assess the contribution of M1 to the two value-based processes (learning and decision making). More precisely, the experiment will extend over three sessions, each occurring at 24-hours interval. Each experimental session will consist of six

blocks, each lasting about 4 minutes. Pilot data suggest that the value-based process begins to effectively shape the subject decisions in the middle of the second session. Given this, cTBS over M1 will be applied either at the beginning of the first session (before learning) or at the beginning of the third session (after learning). This procedure will allow us to disentangle the involvement of M1 in value-based reinforcement learning and value-based decision making.

Disclosures: G. Derosiere: None. **P. Vassiliadis:** None. **S. Demaret:** None. **A. Zenon:** None. **J. Duque:** None.

Poster

620. Human Decision Making: Perception, Motor, and Attention

Location: Hall A

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Topic: F.01. Human Cognition and Behavior

Support: aivoAALTO and Aalto Starting Grant

Title: Neural functions of memory retrieval and narrative reconstruction during free-viewing of film Memento

Authors: *J. E. KAUTTONEN[1], Y. HLUSHCHUK[1], U. HASSON[2], I. JÄÄSKELÄINEN[1], P. TIKKA[1];
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Abstract: To study memory retrieval as an essential part of human cognition and narrative reconstruction, we collected fMRI data during free-viewing of a non-linear puzzle film 'Memento' (2000, dir. C. Nolan, 106 min). In the film, 22 sequences of the story are presented in an inverse order (from end to the beginning) to simulate the experience of the protagonist who suffers of a memory defect (anterograde amnesia). From those 22 sequences, we selected 15 identically structured scenes which are repeated twice during the film at different timepoints. Our hypothesis was that the second repetition of the scene creates a special "anchor-point" (key-frame) that allows reconstruction of the story based on new information that was not previously available. fMRI data was collected with a 3T MRI scanner with TR=1.56s, resulting in 4107 EPI volumes. Analysis included data from 12 healthy subjects (4 males) with the mean age 27 years. Mental state and comprehension of the story were verified using a post-stimulus questionnaire. Data was analyzed with independent component analysis (ICA), searchlight-based multivoxel pattern analysis (sl-MVPA) and representational similarity analysis (RSA) methods. We used the key-frame segments (6-12s time-windows) and their visually identical counterparts to build two

30x30 dissimilarity matrices for a 'higher-level' (A) and 'lower-level' (B) cognitive models. For model A we assumed greater mutual temporal and spatial BOLD signal similarity during all (visually different) key-frame moments, while for model B greater pairwise similarity was assumed only for the key-frames and their (visually identical) counterparts. Both models were tested with activation patterns and independent component time-courses of each subject. Our searchlights analysis included the whole grey matter and 50 components were used for the ICA analysis. For model A, significant correlation was found with regions located at parietal (angular gyrus and precuneus) and frontal lobes (frontal orbital, middle frontal and superior frontal gyrii) with dominance on the right hemisphere. This is congruous with previous studies related to episodic memory recollection and narrative comprehension. In turn, control model B strongly correlated with low-level visual areas which was expected for the visually identical segments. By exploiting the unique narrative structure of Memento, this study demonstrates the feasibility of using naturalistic stimuli and multivariate methods to study complex neural processes related to narrative comprehension.

Disclosures: J.E. Kauttonen: None. **Y. Hlushchuk:** None. **U. Hasson:** None. **I. Jääskeläinen:** None. **P. Tikka:** None.

Poster

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Dana Foundation

Title: The role of the alpha rhythm in regulating neuronal dynamics

Authors: *S. HAEGENS[1], C. B. MIKELL[2], E. H. SMITH[2], J. F. RUSSO[2], T. B. NELP[2], G. P. BANKS[2], S. SINHA[3], S. SHETH[2];
[1]Dept. of Psychiatry, [2]Dept. of Neurolog. Surgery, Columbia Univ. Med. Ctr., New York, NY; [3]UMDNJ Med. Sch., Rutgers Univ., Newark, NJ

Abstract: The alpha rhythm (8-14 Hz) is thought to reflect a mechanism of functional inhibition, regulating the engagement and disengagement of neuronal populations based on task demands. Broadband activity in the high gamma range (70-150 Hz) is considered a correlate of multi-unit

activity. Taking these two signals, we track activity across a range of cortical areas using electrocorticography recordings in human patients with intractable epilepsy (N=18) performing the Multi-Source Interference Task. This task, a Stroop-like paradigm with Simon and Eriksen flanker distraction elements, allows us to address various cognitive aspects including attention, perception, decision-making and the subsequent motor response. We analyzed recordings both from grid electrodes placed over various cortical areas including frontotemporal and parietal cortex, and depth electrodes in prefrontal regions, including the cingulate cortex. Here we address several outstanding issues regarding the functional role of the alpha rhythm. We find a negative relationship between alpha power and broadband (high gamma) activity. Combined, these activation patterns reflect temporal tracking of task-engaged regions, with alpha decrease and broadband increase locked to specific task aspects. We report different types of responses, distributed over cortex, including sites that only respond to the stimulus presentation, sites that only respond to the decision report and/or the feedback, and interestingly, sites that track the time on task. The latter allows prediction of behavioral performance in terms of reaction times. Furthermore, we find a small subset of sites that show modulation with task difficulty, predominantly in temporal areas, and modulation based on task history (whether there was a condition switch from easy to hard trials or vice versa). Taken together, our results further support the notion that alpha reflects functional inhibition at the local neuronal population level, while broadband high gamma activity reflects neuronal activation. Crucially, the combination of these signals allows us to predict behavioral performance. We provide evidence for the generality of this mechanism across cortical areas, including prefrontal cortex.

Disclosures: **S. Haegens:** None. **C.B. Mikell:** None. **E.H. Smith:** None. **J.F. Russo:** None. **T.B. Nelp:** None. **G.P. Banks:** None. **S. Sinha:** None. **S. Sheth:** None.

Poster

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Title: Visual-spatial category encoding in human parietal cortex

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Abstract: Categorization is a fundamental cognitive process by which the brain assigns meaning to incoming sensory stimuli. The higher cognitive functions have traditionally been considered the domain of prefrontal areas. However, recent non-human primate studies have increasingly focused on the essential role of the posterior parietal cortex (PPC), especially the lateral intraparietal (LIP) area, in categorization. Previous work showed that PPC played a central role in spatial attention and saccadic eye movement, and more recent work has found categorical signals in LIP. However, whether human PPC is also involved in visual category remains unclear. Here, using multiple voxel pattern analysis (MVPA) on data from functional magnetic resonance imaging (fMRI) visual-spatial category experiments, we show that activity in human IPS1/2-an area shares similar response characteristics to macaque area LIP-can reflect the groups of spot visual stimulus. Moreover, the activity of human IPS1/2 selectivity shifted markedly with retraining. These findings indicate that human IPS1/2 is involved in human visual-spatial categorization.

Disclosures: **Y. Li:** None. **L. Wang:** None. **X. Hu:** None. **Y. Yu:** None.

Poster

620. Human Decision Making: Perception, Motor, and Attention

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Topic: F.01. Human Cognition and Behavior

Support: NSF grant BCS-1439188

Title: Deciding where to attend: Increased frontal theta/delta oscillations and their neuronal substrate

Authors: *A. RAJAN[1], Y. LIU[2], H. HUANG[1], J. BENGSON[2], G. MANGUN[2], M. DING[1];
[1]J. Crayton Pruitt Family of Dept. of Biomed. Engin., Univ. of Florida, Gainesville, FL; [2]Ctr. for Mind and Brain, Univ. of California, Davis, CA

Abstract: We examined the volitional aspects of attentional control by recording simultaneous EEG-fMRI from subjects performing an instructed/willed visual spatial attention paradigm. Each trial started with a cue. Following a random time delay the target in the form of a spatial grating

was presented and the subject discriminated the spatial frequency of the grating. In the instructed attention condition, the cue directed the subject's attention to either left or right hemifield, whereas in the willed attention condition, the cue prompted the subject to choose the side of the visual field to attend. It is hypothesized that willed attention is accompanied by an increased need for conflict resolution and cognitive control. Consistent with the hypothesis we found that: (1) 600 ms following cue onset a significant increase in theta/delta band (2-6Hz) power in the frontal areas was observed for the choice condition as compared to the instruction condition, and (2) increased theta/delta coherence between frontal and parietal areas was found for the choice condition. Moreover, correlating theta/delta power with concurrently recorded BOLD, it was further demonstrated that the frontal theta/delta activity is likely generated and modulated by a neuronal network including the dorsal anterior cingulate region

Disclosures: A. Rajan: None. **Y. Liu:** None. **H. Huang:** None. **J. Bengson:** None. **G. Mangun:** None. **M. Ding:** None.

Poster

620. Human Decision Making: Perception, Motor, and Attention

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Topic: F.01. Human Cognition and Behavior

Support: CIHR #MOP-97944

Title: Human premotor cortex is implicated in the evaluation of the correctness of observed non-motor visual stimulus sequences according to a learned conjunction rule: a magnetoencephalography study

Authors: L. LUNEAU[1], ***J. F. KALASKA**[2];
[1]Univ. de Montreal, Montreal, QC, Canada; [2]Univ. De Montréal, Montréal, QC, Canada

Abstract: Active human sensorimotor behavior evokes widespread changes in oscillatory brain activity, such as beta rhythm (15-30Hz) suppression during the planning and execution of arm movements and post-movement rebound in motor (M1) and premotor (PM) cortex (Kivalik 2011). The intensity of beta desynchronization varies with directional uncertainty during movement planning (Tzagarakis et al., 2010). The discovery of "mirror neurons" also implicated PM in higher cognitive functions such as the interpretation of observed motor actions. Cisek & Kalaska (2004) found that dorsal PM neurons discharged when monkeys observed the visual cues of a learned motor task and that the activity predicted correct outcomes and signaled

incorrect outcomes. Similarly, Koelwijn et al (2008) reported a stronger beta rebound when human subjects observed an actor making mistakes in a motor task than in correctly performed trials. In all of these cases, PM was activated while subjects observed familiar motor actions or stimulus events associated with learned motor tasks. We examined if PM is also active when subjects observe sequences of visual cues not previously associated with any motor actions while a computer performs a 2-choice target selection task guided by a color-location matching (CLM) rule (Cisek & Kalaska 2005) and interpreted whether the observed events respected the rule. We recorded PM beta activity using MEG in 2 subject groups. Group 1 learned the CLM rule by observation: they watched a computer perform the task correctly or incorrectly (condition 1), and then counted correct or incorrect trials in further trial blocks. In a second session, they actively performed the task with a joystick (condition 2). Group 2 learned by action: they learned the CLM rule by trial and error while performing the task actively in the first session, and then did blocks of the active task (condition 2). In a second session they observed the computer perform the task and counted trial outcomes (condition 1). We recorded 3 Group 1 and 3 Group 2 subjects. We observed typical beta suppression/rebound in both Groups when they actively performed the task (condition 2), and also in Group 2 when they subsequently observed the task (condition 1). Critically, we also found beta suppression/rebound in Group 1 subjects when they observed the task (condition 1) before ever performing it actively. In both Groups, the strength of beta rebound differed for observed correct versus incorrect task performance by the computer. These findings support a role for PM in the cognitive act of interpreting the "correctness" of observed arbitrary sensory events even when they have not been associated with any specific motor actions.

Disclosures: **L. Luneau:** None. **J.F. Kalaska:** None.

Poster

620. Human Decision Making: Perception, Motor, and Attention

Location: Hall A

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Topic: F.01. Human Cognition and Behavior

Support: BCS-1358955

Title: Investigating the plasticity of perceptual decision-making in the human brain

Authors: C. DEVINE[1], D. MCGOVERN[1], S. KELLY[2], *R. G. O'CONNELL[1];
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Abstract: A considerable body of research has established that it is possible to improve perceptual performance through training (Lu et al., 2011) but the precise neural adaptations that give rise to these improvements have yet to be identified. The present study employs a recently developed non-invasive electrophysiological paradigm for isolating neural signals representing each of the three key levels of information processing that are necessary for making simple perceptual decisions (Kelly & O'Connell, 2014). Healthy subjects (N=6 – data collection ongoing) were trained to judge the relative contrast of two superimposed gratings over 5 separate sessions (500 trials/10 blocks per session). The two grating stimuli were flickered at 20Hz and 25Hz respectively, generating distinct steady state visual evoked potentials (SSVEP) whose subtraction indexes the representation of 'sensory evidence'. In addition we tracked the accumulation of this sensory evidence into distinct domain-general and effector-selective decision variable signals. The role of attentional state in learning was also examined by monitoring changes in posterior alpha-band (8-14Hz) activity. Stimulus difficulty was determined individually for each subject prior to training such that baseline performance was approximately 70%. Feedback was given on a trial-by-trial and block-by-block basis and electroencephalography (EEG) was recorded during all training sessions. There was a significant improvement in accuracy across all blocks ($F(49, 196) = 2.65$, $p<.005$) and a reduction in RT that approached statistical significance ($F(49, 196)=1.4$, $p=.056$). Our neural signal analyses will establish whether these behavioural improvements arise from enhanced encoding of sensory 'evidence', changes in the parameters of the neural decision process, changes in motor preparation, changes in attentional engagement or some combination of these factors. zhz

Disclosures: **C. Devine:** None. **D. McGovern:** None. **S. Kelly:** None. **R.G. O'Connell:** None.

Poster

620. Human Decision Making: Perception, Motor, and Attention

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Program#/Poster#: 620.11/W43

Topic: F.01. Human Cognition and Behavior

Title: Attention-related brain potentials predict willingness to pay

Authors: ***N. GOTO**, M. MORTAZAVI, M. WATABE, A. SCHAEFER;
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Abstract: It is often assumed that purchasing decisions are influenced by consumers' Willingness To Pay (WTP), that is, that maximum amount of money that a consumer accepts to pay for a given product or service (Ajzen & Driver, 1992). However, little is known about the

neural and cognitive underpinnings of WTP-driven decisions (Plassmann et al., 2007). The main purpose of this study was to examine with brain event-related potentials (ERP) whether such decisions recruit attentional and cognitive control processes, or if they can rely solely on preattentive mechanisms. In a simulated shopping task, 47 participants viewed a series of pictures of 40 desirable products while scalp EEG was recorded. They were offered 10 different prices for each product consecutively, and their task was to accept or decline each offer. If the highest accepted offer exceeded a "true" price undisclosed to the participants, then participants were given a chance to actually buy this product. The highest accepted offer was coded as their WTP. Offers under WTP were coded as underpriced (UP) whereas those above were coded as overpriced (OP). Results showed that response times were longer for WTP offers compared to both OP and UP offers. Next, we observed a larger frontal positive slow wave for WTP offers compared to both UP and OP and a larger late posterior complex for WTP offers compared to OP offers. Overall, both the behavioural data and the spatio-temporal properties of the ERP results suggest that WTP-driven decisions recruit sustained attentional and working memory (WM) processes. Specifically, it is possible that, in a shopping environment, buying decisions driven by WTP require the active maintenance of a set level price in WM and a continuous comparison of this figure with actual prices. In addition, these findings also indicate that attention-related ERPs are potentially useful tools to model price-driven choices. References: Ajzen, I. & Driver, B.L. (1992). Contingent Value Measurement: On the Nature and Meaning of Willingness to Pay. Journal of Consumer Psychology, 1(4), 297-316 Plassmann, H.; O'Doherty, J. & Rangel, A. (2007). Orbitofrontal Cortex Encodes Willingness to Pay in Everyday Economic Transactions. The Journal of Neuroscience, 27(37):9984 -9988

Disclosures: **N. Goto:** None. **M. Mortazavi:** None. **M. Watabe:** None. **A. Schaefer:** None.

Poster

620. Human Decision Making: Perception, Motor, and Attention

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Topic: F.01. Human Cognition and Behavior

Title: Arousal decreases conservativeness in a random dot motion decision making task

Authors: *W. TORGERUD[1], D. MUSSACK[2], T. LEE[4], G. MAFFEI[5], G. COTUGNO[6], P. SCHRATER[3];
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Santa Barbara, CA; [5]Univ. Pompeu Fabra, Barcelona, Spain; [6]King's Col. London, London, United Kingdom

Abstract: Emotional arousal, a key factor often used to characterize and describe emotions, gears up the body to react to stimuli in the environment. Arousal could functionally accomplish this either by increasing attentiveness or by decreasing conservativeness. Increasing attentiveness effectively increases the rate at which the brain processes incoming perceptual information. Alternatively, an individual who is being less conservative in a decision would be comparatively more willing to act on less evidence. In this pilot study we sought to determine the effects of arousal on decision making by using a two alternative forced choice random dot motion coherence task analyzed with a Bayesian hierarchical drift diffusion model (HDDM). Subjects were exposed to trials consisting of one of three different levels of arousal immediately preceding performance on a random dot motion decision making task. The effect of arousal on decision making was modeled as a constant term modulating perceptual evidence accrual rate, decision threshold boundary (conservativeness in response), both, or neither. These four models were compared using hierarchical Bayesian estimation to determine which best fit the data. The hierarchical nature of the model allowed us to compare data both within and across subjects. Biometric data including galvanic skin response (GSR), heart rate (HR), eye tracking, and automatic recognition of facial emotional expression data were collected for each participant during the experiment. This expansive set of biometric data not only enabled us to validate the effectiveness of our arousal stimuli, but importantly, enabled us to derive our emotional dimensions based upon the tasks and measurements themselves, rather than an a priori assignment of dimensions. Rather than assume that arousal is limited to its effects on heart rate we sought to determine a more complete set of emotional measures. We found that the threshold only model most accurately characterizes the data. This implies that arousal influences decision making by decreasing participants' conservativeness in their responses, rather than by altering the accrual of perceptual evidence via attentional allocation. Biometric validation of our arousal manipulations indicates that the biological measures that predict the level of arousal for each stimulus also predict reaction time. In addition, the emotion data could be used to extract a simple signature of arousal which predicts reaction time on a trial-by-trial basis, seconds before the decision is actually executed.

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Poster

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Support: SFI Grant 09-RFP-NES2382

NSF Grant BCS-1358955

Title: Early target selection signals predict the onset and rate of evidence accumulation during perceptual decision making

Authors: *G. LOUGHNANE[1], D. NEWMAN[2], M. BELLGROVE[2], E. LALOR[1], S. KELLY[3], R. O'CONNELL[1];
[1]Trinity Col., Dublin, Ireland; [2]Monash Univ., Melbourne, Australia; [3]Univ. Col. Dublin, Dublin, Ireland

Abstract: Since it is rarely possible to predict precisely when and where goal-relevant information will present itself, adaptive decision making is heavily reliant on an ability to select motivationally salient sensory events for preferential processing - a phenomenon typically referred to as attentional orienting. To date, research on the critical neural dynamics underpinning orienting and perceptual decision making has proceeded largely in parallel and we still know little about how these two core brain systems interact. Recent work on human EEG has isolated a centro-parietal positivity (CPP) that provides access to the distinct parameters of the neural decision process (e.g. onset time, evidence accumulation rate and decision threshold). In the present study, we probed the impact of early target selection mechanisms on this process. Participants performed elementary perceptual discriminations with and without foreknowledge of the timing and/or location of relevant sensory information. This approach allowed us to identify an early target-selection signal that immediately preceded the onset of the neural decision making process, peaking at approximately 280ms after evidence onset over bilateral visual areas. The selection signal was maximal contralateral to the location of the physical evidence, was exclusively evoked by goal-relevant sensory changes and determined the timing and accuracy of upcoming perceptual reports by modulating both the onset and rate of evidence accumulation during decision formation. These data provide novel insights into the manner in which attention orienting supports decision making in an uncertain environment.

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Poster

620. Human Decision Making: Perception, Motor, and Attention

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Title: Sensory evoked potentials in human anterior cingulate cortex electrophysiological recordings during a cognitive task

Authors: *A. R. WEISS[1,2], M. J. GILLIES[3], A. L. GREEN[3], J. R. WALTERS[1], T. Z. AZIZ[3]; [1]Neurophysiological Pharmacol. Section, NINDS, Bethesda, MD; [2]Nuffield Dept. of Med., [3]Nuffield Dept. of Clin. Neurosciences, Univ. of Oxford, Oxford, United Kingdom

Abstract: Conflict monitoring and error processing are essential executive functions for adaptation to conflicting information. Neuroimaging studies consistently report activity in the medial prefrontal cortex in cognitively demanding conditions, with the anterior cingulate cortex (ACC) believed to be principally active during action-monitoring processes. It is unclear whether ACC activity increases directly with the receipt of error feedback, or simply acts in the detection of response conflict. Ultimately, ACC basic function remains in dispute. This study aimed to investigate ACC function and the role it plays in human cognition. We analyzed local field potentials from electrophysiological recordings from bilateral ACC in chronic pain patients undergoing implantation of deep brain stimulation electrodes. Patients performed a modified Wisconsin card-sorting task, a test sensitive to shifting and flexibility of attention. Utilizing a pre-existing model of response conflict and error likelihood, we revealed a disconnection between sensory evoked potentials from fast response trials featuring low conflict/high error likelihood and slow response trials/low error likelihood (Alexander and Brown, 2012). We observed that the ACC responds differently to correct and incorrect sensory feedback during trials, featuring distinct patterns of 3-8Hz theta and 13-30Hz beta oscillatory activity. Laterality differences are seen between dominant and non-dominant ACC in the initial reaction to the presentation of stimulus and upon receipt of feedback. Additionally, we found that ACC activity at a given site could fluctuate between states of high and low inter-trial coherence with respect to

the requirements of different stages of the cognitive task. Our data offer a valuable electrophysiological comparison of ACC activity, available in awake behaving humans by no other method, in response to sensory feedback during a cognitive task requiring conflict monitoring, error processing, and a selective motor response. This study is believed to be the first demonstration of sensory-evoked potentials in the ACC, and may offer fresh insight into the role of ACC in decision making and learning processes and on the nature of ACC physiology and pathophysiology.

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Poster

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Topic: F.01. Human Cognition and Behavior

Title: Occurrence pattern of EEG at the on-set of a voluntary movement

Authors: *S. KAWASHIMA[1], A. MORI[2], N. T. MINAKAWA[2], M. TAKAYOSE[2];
[1]Grad. Sch. of Literature and Social Sci., [2]Nihon Univ., Tokyo, Japan

Abstract: It is known in the beta band (13~30 Hz) of electroencephalogram (EEG) studies, the prefrontal area is associated with decision-making. On the other hand, specific frequency (6~7 Hz) in the theta band (3~7 Hz) is called frontal midline theta (Fmθ), and it has been confirmed to be associated with concentration in humans. However, the occurrence pattern of theta and beta bands at the onset of a voluntary movement have not been studied in the 128 channels of electroencephalograph. Therefore, in the present study, we investigated the occurrence patterns of theta and beta bands in at the onset of a voluntary movement. The subjects were eight right-handed healthy male athletes who performed a voluntary movement with a button press of 90 times. The EEGs were recorded on the scalp by 128 channels. The standard electrode during the recording was positioned on the vertex of the head and the grounding electrode was on the Fpz (frontal Midline-Perietal). Recording conditions were defined as follows: 500 Hz as the sampling frequency, 0.1 Hz as a low frequency filter, 200 Hz as a high frequency filter and 100 kΩ or lower as a resistance value between the electrode and the scalp. EEGs are classified into theta, alpha and beta bands, respectively averaged from 5 seconds before the onset of the button press. As a result, the occurrence pattern of the theta band was localized in the midline of the prefrontal and occipital regions from 5 seconds before the button press. On the other hand, the occurrence

pattern of the beta band was especially localized in the prefrontal region from 1 second before. In addition, it was also observed that activity was localized in the occipital region. No activity was found in the prefrontal region of alpha band. The present result suggested that there is a difference between the occurrence pattern of the theta band and the beta band at the onset of a voluntary movement. There is a difference in the projection pathway between the generation source of the theta band and beta band to the prefrontal region and the vassal area in the cerebral cortex.

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Poster

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Support: Trinity College Dublin

Irish Research Council

Title: Functional dissociations between abstract and effector-selective decision signals during delayed perceptual choices

Authors: *D. M. TWOMEY[1], S. P. KELLY[2], R. G. O'CONNELL[1];
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Abstract: Complementary neurophysiological research in the human and non-human brain has identified neural signals that gradually accumulate evidence for decision making. While studies in rodents and monkeys have focused on effector-selective signals that represent the translation of the evolving decision into a specific motor plan, recent research on the human brain has demonstrated that decisions are also represented in a manner that is abstracted from the specific sensory or motor requirements of a task. These observations raise critical questions about the functional distinctions between abstract and effector-selective decision signals. Monkey neurophysiology has revealed that effector-selective decision signals remain at an elevated level when a delay is imposed between decision commitment and response execution. This observation has directly informed the model assumptions employed in functional neuroimaging

studies seeking to identify domain-general decision making regions. However, it has yet to be determined whether abstract decision signals exhibit the same sustained activity under delayed response conditions. In the present study, participants performed a variant of the prototypical random dot motion task in which they discriminated the direction of coherent motion in a dot kinetogram but did not indicate their decision until a delayed response cue appeared. This approach enabled us to vary the stimulus-response association. In the 'fixed' condition participants knew that the press required at cue onset always corresponded to the direction of the coherent motion. However, in the 'varied' condition they had to wait for the response cue to find out which hand they should use to report on a given motion direction. We traced the dynamics of abstract and effector-selective decision variable signals in the form of the broad-band centro-parietal positivity (CPP) and limb-selective beta-band activity, respectively. Our results reveal that, while effector-selective signals are sustained during the interval between decision and response, the abstract decision signal returns to baseline following commitment. Furthermore, we find that while effector-selective signals only represent the evolving decision when the stimulus-response association is known in advance, the abstract signals were unaffected by this manipulation. Our findings highlight fundamental functional dissociations between effector-selective and abstract decisions signals and will have important implications for functional neuroimaging investigations of decision-making.

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Poster

620. Human Decision Making: Perception, Motor, and Attention

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 620.17/X1

Topic: F.01. Human Cognition and Behavior

Support: Research Fellow of the Japan Society for the Promotion of Science

Title: Risk-taking decision in motor task can be modulated by transcranial direct current stimulation over dorsolateral prefrontal cortex

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Abstract: Recent studies have demonstrated that human motor decision making under risk tends to be suboptimatl as well as economic decision. However, it remains unclear what brain activity

induces this suboptimality. Right dorsolateral prefrontal cortex (DLPFC) plays a role in the inhibitory control of seductive options. It has been shown that activation in the right DLPFC which induces to increase such inhibitory control leads to safer economic decision making. Here, we investigated whether activation in the right DLPFC with transcranial direct current stimulation (tDCS) reduces risk taking behavior in motor decision task. Participants (N = 12) performed a novel motor decision task in two experimental sessions with three different stimulation protocols. Each experimental session consists of a pre-test and a test during stimulation. The participants randomly received either anodal stimulation over the right DLPFC and the cathodal stimulation over the left DLPFC, cathodal stimulation over the right DLPFC and the anodal stimulation over the left DLPFC, and sham stimulation. The order of stimulation protocols was balanced across the participants and it was double-blinded for the participants and the experimenter. The intensity of stimulation was 2 mA and the stimulation lasted for 20 minutes. The task required the participants to make a decision when to press a button to maximize a total gain of 50 trials in each session. They were rewarded with higher gain if they respond closer to a target time (2300ms) but they had no gain if thy responded after the target time (miss trial). In this task, optimal mean response time that maximizes the total gain was calculated depending on each participant's variability in response time. Therefore, the participants were required a decision considering both own variability in motor output and risk of zero gain. We confirmed risk taking behavior in the pre-test of all three protocols. The average observed mean response time across the participants was 2124±75 ms, although the average optimal mean response time was 1995±44 ms. Compared with the pre-test, this discrepancy was significantly decreased only in the test during anodal stimulation over the right DLPFC and the cathodal stimulation over the left DLPFC (pre-test = 129±83 ms, test during stimulation = 87±69 ms, $p < .01$). The numbers of miss trials also decreased in the test during stimulation more than the pre-test (pre-test = 7.0±4.7 trials, test during stimulation = 5.5±3.5 trials, $p = .082$). Other two stimulations did not significantly influence the participant's behavior. These results indicate that the activity in the DLPFC is related to risk-taking behavior in motor decision making.

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Poster

620. Human Decision Making: Perception, Motor, and Attention

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Topic: F.01. Human Cognition and Behavior

Title: Modeling of generation of self-organized response in the analog circuit from dynamic memories coded on the neural network using multi-scale biological oscillations

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Abstract: Objective In biological systems, water, nucleic acid, and protein molecules realize various properties and important functions derived from of hydrogen bonds with natural frequency (ca. 1,000,000,000,000Hz). Although a semiconductor memory presents a memorizing function using flip-flop, which keeps the output state by feedback of the input one, it may be possible that biological systems construct a memory circuit using multi-scale oscillations including this intrinsic frequency band. Here we investigate a neural mechanism of decision making by designing the circuit based on our assumption that a memory is coded in a dynamic state of a network using multi-scale biological oscillations, and a self-organized response is generated by phase modulation in the brain analog circuit. Methods Previous findings indicate that sensory inputs do not induce an action potential but locks the inner state of a spontaneous-firing system by phase modulation [1-2]. According to this idea in order to implement a memory-storing state, we design an oscillating analog circuit that realizes the probabilistic metastable transition state among multiple modes with different phase and frequency, and verify its properties. Results Defining the transition from a probabilistic state to a locked one as a phase transition in this circuit, it can be thought that the metastable transition state is at the critical state toward the locked one. This critical state is stable to small perturbation and low noise. Therefore this strategy is an effective way to control noise in analog systems which are susceptible to it. A series of observed performances show that it is possible to retain memory in a probabilistic transition mode and recall in a locked mode by synchronization triggered by input signals. It is suggested that we will be able to obtain a self-organized response such as the activation of specific circuits by diffusion of locked states in networks, if a circuit is designed to induce further synchronization for significant outputs using amplifier circuits and so on. Conclusions It is expected that the progress of the research on the control mechanism using multi-scale oscillations, including the natural frequency band of hydrogen bonds, will bring the breakthrough of technologies such as information processing or prediction of social behavior based on the decision making algorithm. 1. T. Kenet et al., Nature, vol. 425, pp. 954-956, 2003. 2. J. Fiser et al., Nature, vol. 431, pp. 573-578, 2004.

Disclosures: **M. Hirabayashi:** None. **H. Ohashi:** None.

Poster

620. Human Decision Making: Perception, Motor, and Attention

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Title: Temporal dynamics of activity in human anterior cingulate cortex during an event-related color-word Stroop interference task

Authors: *K. L. ANDERSON[1,2], V. PIAI[1,2], J. J. LIN[3], R. T. KNIGHT[1,2];
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Abstract: It is well established that anterior cingulate cortex (ACC) is an important node in the cognitive control network, though its specific contributions are still under debate. ACC has been found to be active during performance of the Stroop task in many neuroimaging studies, and this region is believed to be involved in cognitive conflict processing. However, to what extent this activity involves conflict detection and resolution, error detection and correction, and more generally, regulation of selection processes is unresolved. We recorded electrical activity (electrocorticography; ECoG) from the anterior cingulate of human patients undergoing pre-surgical monitoring for intractable epilepsy while they performed a classic Stroop task. The task employed an event-related design, with congruent (same color), incongruent (different color), and neutral (non-word) stimulus conditions randomly interspersed. Patients were instructed to respond as quickly and accurately as possible by naming the color of the stimulus. Behaviorally, the fastest response times occurred for neutral stimuli, followed by congruent, and then incongruent trials. Based on the prevailing hypothesis positing the ACC's involvement in conflict detection, we predicted greater high-gamma band (HG, 100-250 Hz; a marker of cortical activation) activity in ACC electrodes following incongruent trials, compared with congruent trials. However, while robust task-related activation in the high gamma band between 200ms and 500ms relative to a pre-stimulus baseline was observed in anterior cingulate electrodes, no consistent differences were found between the neutral, congruent and non-congruent conditions. Our ECoG results provide support for the role of the ACC in continuous top-down regulation of selection processes. However, the lack of condition effects in this event-related design,

controlling for arousal, challenges the notion that the ACC is specifically involved in conflict resolution.

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Poster

620. Human Decision Making: Perception, Motor, and Attention

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Topic: F.01. Human Cognition and Behavior

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Title: Action selection as a biased competition up to the primary motor cortex

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Abstract: During penalty shootouts, a soccer goalie knows the probabilities associated to each player's shooting side preference. Together with sensory information, this previously cued knowledge is used by the goalie to decide towards which side to dive in order to catch the ball. In this situation, deciding what action (i.e. which side to dive for) to perform has traditionally been explained within the framework of information processing (e.g. Sternberg, 2011). In this view, the soccer goalie would, based on sensory input and probability knowledge, first compute a decision in prefrontal areas, which would subsequently act as input to motor processing yielding the observed action (the dive). Importantly, this view suggests that relevant task factors (e.g. probability of an upcoming action) are integrated in the decision process through a cost/benefit computation implemented at the OFC/vmPFC level (Hare, Camerer, Knoepfle, & Rangel, 2010; Padoa-Schioppa, 2011; Wallis & Miller, 2003). Other authors have emphasized an 'embodied' view on decision-making (Cisek & Kalaska, 2010; Shadlen, Kiani, Hanks, & Churchland, 2008). This evolutionary perspective suggests the involvement of sensorimotor areas in decision-making. Stemming from single-cell recordings in monkey studies and formalized in the affordance competition hypothesis (Cisek, 2007), this competition is suggested to be limited to premotor areas. Recent models of human action selection advocate such a view (e.g. Domenech & Koechlin, 2015). However, in humans, it is not clear up to what level this competition takes place. To formally address this question in humans, we designed a functional Magnetic Resonance Imaging (fMRI) experiment. Participants were shown cues indicating the

probabilities associated with upcoming button presses. If action selection (i.e. pressing the left or right button) is performed through a biased competition in sensorimotor regions, these same regions are expected to integrate relevant task factors (e.g. probability cues). Our results show that the biased competition induced by probability cues is represented up to the primary motor cortex. Specifically, activity in the contralateral primary motor cortex increased with action probability; instead, activity in the ipsilateral motor cortex decreased. This finding strongly suggests that human decision-making derives from a biased competition taking place up to the primary motor cortex.

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Poster

620. Human Decision Making: Perception, Motor, and Attention

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Wi 3767/1-1

Title: Dynamics of evidence integration in canonical models of perceptual decision making

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Abstract: The brain is able to interpret streams of high-dimensional ambiguous information and yield coherent percepts. This process of evidence integration has been studied extensively [1] but the underlying neuronal network dynamics remain largely unknown. Several models can explain the behavioral performance in these tasks [1,2], although they rely on different dynamical mechanisms. Here, we characterize the dynamics of evidence integration using three canonical one-dimensional models: (1) the Drift Diffusion Model (DDM), (2) the Perfect Integrator (PI)

and (3) the double-well potential (DW) which captures the dynamics of the attractor networks[3]. We examined the categorization dynamics of these models in response to fluctuating stimuli of different duration seeking contrasting and experimentally testable predictions. Stimuli are drawn from a Gaussian distribution $N(\mu, \sigma)$ and the two stimulus categories are defined by $\mu > 0$ and $\mu < 0$. We find that the models behave differently in response to stimuli with different σ: In the small σ regime, both the DW and the DDM perform transient integration and exhibit a decaying psycophysical kernel (PK) revealing a primacy effect (i.e. only the first part of the stimulus is used for classification). In the large σ regime, the effective integration window in the DDM decreases because the absorbing bound is reached earlier. In contrast, the DW allows for classification reversals whose rate increases with σ producing a change in the PK time course from decreasing to increasing (recency effect). The PI shows constant PK for all σ's (i.e. uniform integration). The discrimination sensitivity(β) in the PI and the DDM decreases monotonically with σ because the two stimulus categories become less separable and because of the reduction in effective integration time in the DDM. Remarkably, the β in the DW as a function of σ shows a local maximum at $\sigma max > 0$. This “stochastic resonance” phenomenon allows some correcting reversals (i.e. transitions to the deeper well) to compensate for the decrease in stimulus separability. Finally, we also find that the models behave differently with σ when the initial condition is offset, what can represent unequal prior probabilities of the two categories: the choice bias caused by the offset decreases with σ in the DW, increases in the DDM and remains constant in the PI. Our analysis makes strong specific predictions to be tested in psychophysical two alternative forced-choice tasks which would pin down the basic principles of sensory integration dynamics. References 1.Gold, Shadlen. Annu. Rev. Neurosci. 30, 535-574 (2007) 2.Wang. Neuron 36, 955-968 (2002) 3.Roxin, Ledberg. PLoS Comput Biol 4, e1000046 (2008)

Disclosures: **G. Prat Ortega:** None. **K. Wimmer:** None. **J. de la Rocha:** None. **A. Roxin:** None.

Poster

620. Human Decision Making: Perception, Motor, and Attention

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Topic: F.01. Human Cognition and Behavior

Support: Dana Foundation

NIH EY13692

Title: Computational modeling reveals differences in how patients with Parkinson's disease implement bias in perceptual decision-making compared to healthy control subjects

Authors: *M. A. BASSO[1], A. PERUGINI[1], J. DITTERICH[2];
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Abstract: Patients with Parkinson's disease (PD) as well as a group of age-matched healthy controls (HC) made perceptual judgments about the orientation of dynamic Glass patterns in a two- alternatives forced choice task. Signal strength (coherence) was varied randomly from trial to trial, and choices and response times were recorded. Subjects initially experienced a block of trials with the two possible orientations being presented with equal probability (50:50), followed by a block of trials with unequal priors (80:20) and then a final block with again equal priors (50:50). In this simple task we found that both HC and patients with PD were able to track the priors. Decisions were affected by the prior information, in particular when the sensory evidence was weak. We found interesting differences in how the decision process was affected by the prior information in patients versus HC. We used the drift-diffusion modeling framework to determine how healthy control subjects and patients with PD implemented the decision bias. Within this framework, there are two possible ways decision bias can be generated: 1) a starting point of evidence accumulation that is closer to one decision boundary than to the other or 2) a drift rate offset, meaning that the process drifts towards the boundary associated with the more frequent choice even in the absence of any sensory evidence. The two ways of implementing bias have different consequences for decision times and can therefore be distinguished based on response time data. Modeling the data revealed that HC's starting point closely tracked the priors, whereas their drift rate offset was undergoing only smaller and slower changes. In contrast, PD patients tracked the priors primarily with a drift rate offset, whereas their starting point of evidence accumulation was undergoing only smaller and slower changes. Thus, while both groups were able to track the priors, they apparently used different mechanisms to do so. We propose that the effective adjustment of the starting point of evidence accumulation requires intact basal ganglia.

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Poster

620. Human Decision Making: Perception, Motor, and Attention

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Support: Dana Foundation

NIH EY13692

Title: Faulty use of prior information in patients with Parkinson's disease

Authors: *A. PERUGINI[1], J. DITTERICH[3], M. A. BASSO[2];
[2]Psychiatry and Neurobio., [1]UCLA, Los Angeles, CA; [3]Ctr. for Neurosci. and Dept. of Neurobiology, Physiol. & Behavior, UC Davis, Davis, CA

Abstract: When sensory information is ambiguous, we make perceptual choices based on information that was previously learned about the stimulus. Many studies show that the basal ganglia (BG) are necessary for learning stimulus outcome relationships based on feedback, but little is known about their role in using this learned information to make decisions. In other words, how are memories acquired through experience used to make decisions? Our hypothesis is that the BG makes already established memories available to drive choices of actions that are not value or reward based. To test this idea, we developed a 2-alternative forced choice task in which patients with Parkinson's disease (PD) and healthy subjects (HC) make choices about the orientation of Glass patterns. We manipulated the levels of visual information contained in the stimulus (coherence) and also the statistics of the stimulus by making one orientation more probable then the other (prior). We have shown that patients with PD can learn the unequal priors associated with a stimulus orientation if the prior is strong (yet implicit) and that they can use it to make decisions when sensory information is not available: both HC and patients with PD learned and used the prior (N = 10 control vs bias: $p < .05$); but patients with PD did not use it optimally, rather they perseverated (Perugini et al. Abstract SFN 2014). These preliminary data suggested that the impairment in patients with PD is not in learning the prior, but rather in using it. Here, we conducted new experiments to directly test this hypothesis. First, we modified our task and made the implicit prior less obvious by presenting two randomly interleaved stimuli, one associated with an equal prior (50:50) and the other with an unequal prior (75:25). Subjects computed two different stimulus statistics simultaneously and used them to make choices. We found that whereas HC used the prior correctly when sensory information was uncertain (N = 14 control vs bias: $p < .05$), patients with PD failed to do so (N = 14 control vs bias: $p > .05$). Second, we informed patients about the presence and the type of the prior explicitly before the start of the experiment to exclude the possibility that the deficit in patients was in using the priors and not in learning them. Under these conditions, subjects do not need to learn the priors associated with the stimuli, their only task is to use the information provided to make their choices. We found that patients with PD were impaired in this task when learning was not required (N = 7 control vs bias: $p > .05$). Altogether our data support the hypothesis that patients with PD are impaired in accessing memory information that was previously learned to guide decisions.

Disclosures: A. Perugini: None. **J. Ditterich:** None. **M.A. Basso:** None.

Poster

620. Human Decision Making: Perception, Motor, and Attention

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 620.24/X8

Topic: F.01. Human Cognition and Behavior

Title: Influence of value-dependent endogenous signals on saccadic choice

Authors: *E. CHU[1], L. M. HARRIS[1], V. W. LEE[1], S. FARASHAHI[2], A. SOLTANI[2]; [2]Psychological & Brain Sci., [1]Dartmouth Col., Hanover, NH

Abstract: Saccadic target selection is one of the most frequent decisions made by the nervous system. Every saccade is determined by both external factors, such as the onset time or the physical salience of visual stimuli, as well as internal factors, such as reward expectation. While much is known about how external factors determine target selection, neuroscientists have only recently begun to explore the contribution of internal factors to saccadic choice. Here, we used a modified version of the paired-target task to study the differential effects of value-dependent endogenous signals on saccadic target selection. The two targets (Gabor patches), which could be visually similar or dissimilar, appeared on a computer screen with varying onset asynchrony (TOA). In two sets of experiments, subjects reported what they perceived to be the first of two targets to appear on the screen by making a saccadic eye movement to it. During experiment 1, when the two targets were visually identical, the amounts of reward/gains and punishment/losses associated with correct or incorrect detection on each side of the fixation cross were cued at the beginning of every trial. In experiment 2, when the two targets were different, subjects performed the same type of visual selection but in the absence of any external cues. In this experiment, amounts of gains and losses associated with correct and incorrect responses were based on target identity, and were already learned by the subject. Additionally, we measured subjects' risk and loss aversion by asking them to choose between pairs of gambles with varying amounts of gains/losses and probabilities. Our results were threefold. First, we found a stronger bias (by two-fold) in target selection toward the target that yields a larger gain compared with the one that yields a smaller loss, even when the magnitudes for gains and losses were similar. Nevertheless, the amounts of bias for gain and loss manipulations were correlated within each subject. Moreover, the amounts of bias were equal in both experiments, reflecting that spatial top-down attention was not critical for the observed shifts in behavior. Secondly, we observed an improvement in sensitivity to the TOA for the more rewarding target in both gain and loss manipulations in experiment 2, but not in experiment 1. These results indicate that distinguishable targets associated with different amounts of gains and losses could evoke

differential response onset. Finally, we did not find any correlation between the magnitude of bias in target selection and individual risk/loss aversion, suggesting that the effects of reward on target selection could be independent of reward preference in economic choice.

Disclosures: E. Chu: None. **L.M. Harris:** None. **V.W. Lee:** None. **S. Farashahi:** None. **A. Soltani:** None.

Poster

620. Human Decision Making: Perception, Motor, and Attention

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Program#/Poster#: 620.25/X9

Topic: F.01. Human Cognition and Behavior

Title: Reward primes representations in human short-term visual memory

Authors: *C. M. HICKEY, M. V. PEELEN;
Ctr. for Mind / Brain Sci., Univ. of Trento, Rovereto, Italy

Abstract: Reward coding in the midbrain is thought to cause the rapid prioritization of reward-associated visual stimuli, but the neural mechanisms that create such incentive salience are largely unknown. We used human fMRI to study how reward feedback might retroactively influence the perceptual representation of naturalistic visual stimuli. Participants viewed briefly presented images of city- and landscapes that contained examples of trees, cars, and people. For each participant two of these three categories were targets that required manual response. Correct performance garnered reward feedback that could randomly have either high or low magnitude. Using multivoxel pattern analysis we found that high-magnitude reward acted both to reinforce target information encoded in visual cortex and to cause the strong suppression of nontarget information. Critically, this occurred in spite of the fact that the visual stimuli were no longer present when reward feedback was received. Reward thus appears to impact short-term visual memories of the scene. Further analyses identified a network of subcortical and cortical brain areas involved in instantiating this effect. The results identify a mechanism through which reward can act to guide human vision, demonstrating a novel interaction between neural systems responsible for reward processing and visual perception in the human brain.

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Poster

620. Human Decision Making: Perception, Motor, and Attention

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Title: 3D reconstructions and quantitative analyses of immunocytochemical staining patterns in the human subthalamic nucleus (STN)

Authors: *A. ALKEMADE[1], M. C. KEUKEN[1], G. DE HOLLANDER[1], R. BALESAR[1], M. WEISS[1], A. TRUTTI[1], A. SCHAEFER[2], B. U. FORSTMANN[1];
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Abstract: With the development of ultra-high field 7Tesla MRI techniques, we can visualize individual brain structures *in vivo* with unprecedented detail. However, the detail obtained is still well above the cellular level, and fine-grained anatomical resolution using post-mortem anatomical staining methods are still considered a prerequisite to fully understand the biological processes within the brain. The present studies are aimed at the integration of post-mortem analyses and noninvasive imaging techniques. For this purpose, a pipeline that allows 3D reconstruction of immunocytochemical staining patterns within the human subthalamic nucleus (STN) was developed. Tissue blocks obtained from patients suffering from Parkinson's disease (PD) and controls were scanned with 7T MRI, and the STN was manually segmented. Tissues were paraffin embedded and blockface imaging was performed during the cutting procedure. After immunocytochemical staining for markers of GABA-ergic, glutamatergic, dopaminergic, and serotonergic signaling, sections were digitized and 3D staining patterns were reconstructed in MNI-standard space using linear and nonlinear registration. Image analyses were performed in ImageJ using thresholding procedures and staining gradients were quantified. The results indicate that the STN is an inhomogeneous structure, and staining patterns differ between immunocytochemical markers. These studies provide novel quantitative insight in the functional neuroanatomy of the human STN.

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Poster

621. Memory and Cognition: Influence by Aging

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Topic: F.01. Human Cognition and Behavior

Support: Grant-in-Aid for Scientific Research (A) (No. 25245068), MEXT KAKENHI, Japan

Title: Neural correlates of working memory for face and location in advanced aging

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Abstract: Working memory declines with age. Previous studies have reported that older adults demonstrated greater and more widespread brain activation than young adults for working memory. The present functional magnetic resonance imaging (fMRI) study investigated whether this pattern of age-related 'over-recruitment' continues into advanced age. During fMRI scanning, two groups of older adults ('young-old'; n=13; 61-70 years and 'old-old'; n=14; 77-82 years) performed an n-back task. Participants were shown with a face or a dot on a screen. In the 0-back task, participants were asked to judge whether the face is female or male for face condition, or whether the dot is located in the center of the screen for location condition. In the 1-back task, participants were asked to judge whether or not the current item was identical to the one immediately preceding it (i.e., the face or the location of the dot presented one trial back). The fMRI data revealed both groups recruited similar networks to support working memory irrespective of material, including the lateral frontal, parietal cortex, and insula. Age-related increase (old-old group > young-old group) in working memory effects for face were found in the right dorsolateral prefrontal cortex (DLPFC) and the bilateral fusiform gyrus, and those for location were shown in the bilateral DLPFC and the left lateral parietal cortex. Among these age-sensitive regions, the bilateral fusiform gyrus and the left lateral parietal cortex also showed material effects (face > location or location > face, respectively). On the other hand, age-related increase in working memory effects in the right DLPFC overlapped across materials. There were no regions where working memory effects was greater in young-old group. Our results demonstrated two main findings. First, age-related over-recruitment of brain activity in working memory continues into advanced age. Second, increased engagement of the right DLPFC, along

with regions involved in the online processing of material information, may serve a compensatory role in mediating working memory function in old-old adults.

Disclosures: **M. Suzuki:** None. **T. Kawagoe:** None. **S. Nishiguchi:** None. **N. Abe:** None. **Y. Otsuka:** None. **R. Nakai:** None. **M. Yamada:** None. **S. Yoshikawa:** None. **K. Sekiyama:** None.

Poster

621. Memory and Cognition: Influence by Aging

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 621.02/X12

Topic: F.01. Human Cognition and Behavior

Support: JSPS Grant-in-Aid for Young Scientists (B) 25870325

Title: The effects of physical exercise with music on prefrontal cortex volume of elderly people: mihama–kiho scan project

Authors: ***K. TABEI**[1], M. SATOH[1], J.-I. OGAWA[2], T. TOKITA[3], N. NAKAGUCHI[4], K. NAKAO[5], H. KIDA[1], H. TOMIMOTO[1];
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Abstract: Physical activity is associated with positive effects on the brain of elderly people. In our previous study (Satoh et al., PLoS ONE, 2014), we indicated that physical exercise with musical accompaniment produced more positive effects on cognitive function in elderly people than exercise alone. However, little evidence is available on neuroimaging data of combining physical exercise with music. This study aimed to explore the dynamics of structural brain changes related to physical exercise with musical accompaniment in normal elderly people. We enrolled 199 participants (age 64-84 years old). Eighty participants performed physical exercise (once a week for an hour with professional trainers) with musical accompaniment (ExM group); eighty participants performed the same exercise without music (Ex group); thirty-nine participants were the control group (Cont group). Before and after a year-long intervention, each participant was assessed by neuropsychological batteries. MRIs were performed before and after intervention. After a year-long intervention, ExM and Ex groups had better intellectual function than Cont group. Furthermore, only ExM group had better visuospatial function than Cont group. Voxel-based morphometry (VBM) analyses revealed significantly (FWE corrected, $p \leq 0.05$) higher gray matter (GM) volume in the superior frontal gyrus in ExM group compared to the

Cont group. On the other hand, Ex group showed significantly (FWE corrected, $p \leq 0.05$) higher GM volume in the insula compared to the Cont group, which in line with the previous neuroimaging studies which have implicated the insula in cardiovascular control. This study adds on previous results, showing that physical exercise with music not only induces positive effects on cognitive function, but also fine-grained neuroanatomical changes in the brain of elderly people.

Disclosures: **K. Tabei:** None. **M. Satoh:** None. **J. Ogawa:** None. **T. Tokita:** None. **N. Nakaguchi:** None. **K. Nakao:** None. **H. Kida:** None. **H. Tomimoto:** None.

Poster

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Topic: F.01. Human Cognition and Behavior

Support: Advancing a Healthier Wisconsin (AHW) FP00005822

National Institute on Aging Training Grant T35 AG029793-08

Title: Neuropsychological and neuroanatomical factors associated with speech-in-noise perception in aging

Authors: *K. A. ALTONJI, J. HANSON, M. KASSEL, C. HUMPHRIES, M. SABRI; Neurol., Med. Col. of Wisconsin, Milwaukee, WI

Abstract: This study sought to determine whether declining speech-in-noise perception in older adults with normal hearing thresholds is associated with cognitive performance (specifically attention and working memory) and structural integrity of cortical gray matter. 18 younger adults (ages 20-41, mean= 26.1, SD= 5.7) and 18 older adults (ages 57-72, mean= 62.4, SD= 4.9) with normal hearing (audiometric thresholds ≤25 dB HL 500 - 4,000 Hz) were tested with the Montreal Cognitive Assessment, the Test of Everyday Attention, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Wechsler Adult Intelligence Scale, and the QuickSIN Speech-in-Noise Test. The QuickSIN involves 12 lists of 6 syntactically correct sentences spoken by a female and masked by four-talker babble presented binaurally through headphones. The sentences are presented at a range of signal-to-noise ratios (SNR) between 25 and 0 dB. Structural Magnetic Resonance Imaging (MRI) scans were acquired in all subjects. On average, older adults performed significantly worse on the QuickSIN 0 dB SNR than the younger

adults ($p < .05$). A multiple regression was performed across both groups with age and RBANS attention tasks as predictors for QuickSIN 0. For this model, raw scores of RBANS attention-digit span (working memory) and RBANS attention-coding (processing speed) were significant predictors of speech perception performance ($p < .001$). Structural analyses revealed, for older adults only, a significant relationship between QuickSIN 0 and bilateral gray matter thickness in regions of the frontoparietal attention network (middle frontal gyrus, superior frontal gyrus, superior parietal lobule, right intraparietal sulcus), semantic network (inferior frontal gyrus, angular gyrus, precuneus, middle temporal gyrus), and speech perception regions (superior temporal sulcus) ($p < .05$). Structural correlations were subject to false discovery rate correction ($q = .05$) for multiple comparisons. This study demonstrates that in aging, speech perception in noise does indeed decline despite normal hearing and that this can be attributed to declining executive function related to attention and working memory. In addition, deficits in speech perception are also associated with decreased gray matter thickness in cortical areas involved in executive cognitive control, attention, and language processing.

Disclosures: K.A. Altonji: None. **J. Hanson:** None. **M. Kassel:** None. **C. Humphries:** None. **M. Sabri:** None.

Poster

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Topic: F.01. Human Cognition and Behavior

Support: NIH grant R01 5R01AG033406

Title: Neural representations of subjective value across the human lifespan

Authors: *M. A. GRUBB[1], S. RASHID[1], P. W. GLIMCHER[1], I. LEVY[2];
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Abstract: Humans often face decision scenarios in which the actual outcome of one or more of the available options is uncertain. Sometimes the probability that an event will occur is known (e.g., a 50% chance of gaining $10), while other times, only partial information is available (e.g., a 25%-75% chance of gaining $10), and our idiosynchratic attitudes to risk and ambiguity, respectively, guide our choices. How these attitudes change across the human lifespan, particularly in more vulnerable phases like adolescence and elderhood, and how the brain

incorporates features like value, risk, and ambiguity to arrive at a unified representation of the subjective value (SV) of a given option is of great interest to economics and neuroscience alike. Here, we evaluate the neural correlates of subjective value representation under uncertainty across the lifespan. 60 participants (12-88 y.o., 35 F) made choices between a fixed reference amount (certain gain of $5) and a lottery whose magnitude ($4-$120), probability of payout (0.25, 0.5, 0.75), and degree of ambiguity (0, 0.24, 0.5, 0.74) was systematically manipulated; neural activity was concurrently measured using fMRI. The SV for each option was modeled using a power utility function with an additional ambiguity-attitude parameter, and choice data were fit with a logistic function to obtain idiosynchratic risk and ambiguity attitudes. One of the choices was randomly selected at the end of the experiment and determined bonus earnings. We examined the timecourse of the BOLD signal in the ventral striatum and the ventral medial prefrontal cortex (vMPFC) using ROI masks from a 2013 meta-analysis of the neural correlates of subjective value. Using individual risk and ambiguity attitude parameters, we calculated the SV of each option and computed trial triggered averages of the BOLD response, separately for two SV conditions (High, Low). A mixed-design ANOVA was performed on the peak activation in each ROI, with SV condition as a within-subjects factor and age group (12-50, 51-90) as a between-subjects factor. In line with previous research, we found that subjective value modulates BOLD activity in the ventral striatum and the vMPFC. We found no evidence for an age x SV interaction, in either ROI, suggesting that SV representation is robust from adolescence to elderhood. We did find, however, some evidence for a main effect of age in the ventral striatum, with the 51-90 group showing a decrease in overall activation relative to the 12-50 group. No evidence for such age related differences were found in the vMPFC. Future analyses will assess more fine-grained age-related differences in the precision of the SV representation in both ROIs.

Disclosures: **M.A. Grubb:** None. **S. Rashid:** None. **P.W. Glimcher:** None. **I. Levy:** None.

Poster

621. Memory and Cognition: Influence by Aging

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Program#/Poster#: 621.05/X15

Topic: F.01. Human Cognition and Behavior

Title: Proactive interference as a source for age related navigational decline

Authors: ***M. MERHAV**[1], T. WOLBERS[2];
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Abstract: Elderly people often report declines in navigational abilities, for example, problems in finding one's way in a new environment. Even though numerous studies have investigated spatial navigation impairments in old age, the mechanisms underlying such deficits are poorly understood. One such mechanism could be Proactive Interference (PI), a situation in which previous learning disrupts the ability to recall more recently presented information. PI could, for example, lead to problems whenever spatial information needs to be updated, for example when having to find your car in a parking lot you frequently visit. Age related PI has been observed both in working memory and in associative learning tasks, but whether such deficits also occur in the spatial domain is unknown. To address this question, we designed an incidental object-location task in which we presented 24 objects, one at a time, to healthy young and old participants (the encoding phase). Each object was presented in a distinctive location. There were no instructions to remember the locations of the objects, but participants were asked to judge the dimensions and colorfulness of each object. In the interference phase, which took place a day before encoding, half of the objects (12) were presented in a different set of locations. In the retrieval phase, which took place two hours after the encoding phase, participants had to indicate the location of each of the 24 objects, as placed in the encoding phase. The distances to the correct locations were calculated to measure retrieval accuracy for the interfered and the non-interfered associations. The results reveal an interaction between interference condition and age group, showing that older participants were selectively impaired at recalling interfered object-locations associations. This result presents PI as a potential source for navigational deficits in elderly people and provides an example for age related deficit in spatial updating.

Disclosures: **M. Merhav:** None. **T. Wolbers:** None.

Poster

621. Memory and Cognition: Influence by Aging

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Title: A modified-Sternberg paradigm measures load and delay components of working memory in cognitive SuperAgers

Authors: *A. H. COOK[1], E. LOYER[1], M.-M. MESULAM[1], S. WEINTRAUB[2], H. BREITER[2], E. ROGALSKI[1], J. REILLY[2];
[1]Cognitive Neurol. & Alzheimer's Dis. Ctr., [2]Psychiatry & Behavioral Sci., Northwestern Univ., Chicago, IL

Abstract: Objective: The Northwestern University SuperAging Program studies individuals over age 80 (SuperAgers) who perform at least as well as middle-age adults on tests of episodic memory in order to identify neurobiologic factors that contribute to successful cognitive aging. Previous research suggests that decline in working memory underlies age-related impairment in episodic memory, possibly due to reduced ability to hold information in working memory. Traditional working memory tasks do not differentiate components of working memory such as the amount of information held (load) and the duration over which it is held (delay). The present pilot study aimed to validate the use of a novel modified-Sternberg task that allows for the differentiation and quantification of working memory components in SuperAgers. **Method**: Four SuperAgers (ages 83-86) and 6 cognitively average Middle-age Controls (ages 57-63) completed a novel computer-based modified Sternberg task that consisted of 4 blocks of 32 trials over which arrays of 1-7 boxes (load) were briefly presented. After a variable delay (1-10 seconds), a probe box appeared and subjects indicated whether the probe was in the same or different location as any box in the preceding array. Response accuracy (hit and false alarm rates), d-prime (sensitivity to detect a correct target among noise), and beta (decision threshold to report a signal) were calculated at each load, as was response time for correct response trials (correct hit or rejection). Repeated Measures General Linear Models were used to compare the groups on each measure. **Results**: SuperAgers did not differ from Middle-age Controls with regard to response accuracy, d-prime, or beta (p's > 0.05). As expected, both groups demonstrated an increase in false alarm rate and beta with increasing load (p's < 0.001) as well as a decrease in d-prime ($p < 0.001$) and trend towards a decrease in hit rate ($p = 0.14$) with increasing load. Both groups demonstrated increased response time with increasing load ($p < 0.001$) yet SuperAgers were significantly slower overall ($p < 0.01$). **Conclusions**: Preliminary results from a novel working memory task suggest that SuperAgers perform as accurately as younger adults on tests of working memory. While performance accuracy was similar between the groups, SuperAgers took longer to make their response, consistent with literature that documents age-related decline in processing speed. Slower response time may reflect a compensatory mechanism that supports the maintenance of cognitive abilities with increasing age. Overall, task demands appear appropriate for continued use in SuperAgers as a means of investigating components of working memory.

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Poster

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Topic: F.01. Human Cognition and Behavior

Support: Northeastern University Undergraduate Research Grants

Title: Cognitive performance and gait task difficulty are predictors of stride variability during dual-task walking

Authors: *L. A. ZUKOWSKI[1], P. PLUMMER[1,2];
[1]Dept. of Allied Hlth. Sci., [2]Human Movement Sci. Curriculum, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Difficulty of cognitive and gait tasks can influence dual-task interference during walking. However, it is currently unknown whether task difficulty can predict gait variability during dual-task performance. Therefore, the purpose of this study was to determine if reaction time variability and/or accuracy during the dual-task performance of gait and cognitive tasks of varying difficulty levels are predictors of spatiotemporal stride variability in young and older adults. METHODS: Twenty-eight healthy, young adults (21.9±1.4 years) and 12 healthy, older adults (73.1±5.6 years) performed six dual-task conditions that included all combinations of two cognitive tasks (from easier to harder: auditory Stroop task, clock task) and three walking tasks (from easiest to hardest: walking at preferred speed, walking at fastest comfortable speed, fast walking while crossing an obstacle). Two linear regressions were utilized with stride time coefficient of variation (CV) and stride length CV as the dependent variables and cognitive task accuracy, reaction time CV, walking condition, cognitive condition, and age group as the independent predictors (α=0.05). To further explore the regression results, a repeated-measures ANOVA was then utilized to compare stride variability for the different age groups, walking conditions, and cognitive conditions (α=0.05). RESULTS: The independent predictors accounted for 55.5% of the variance in stride duration CV. Accuracy in the cognitive tasks (β=-4.868, $p<0.001$) and crossing an obstacle (β=4.846, $p<0.001$) were the strongest predictors of stride duration CV, but age group (β=0.961, $p=0.002$) was also a significant predictor. In the ANOVA, main effects for age ($F=12.177$, $p=0.001$) and walking condition ($F=102.045$, $p<0.001$) were observed as well as an interaction effect between walking condition and age ($F=6.054$, $p=0.005$).

Reaction time CV, walking speed, and cognitive condition did not predict changes in stride duration CV. Finally, stride length CV was not significantly related to any of the tested predictors. CONCLUSIONS: Cognitive performance accuracy, age group and walking task difficulty are significant predictors of temporal but not spatial gait variability. Greater temporal gait variability is associated with lower cognitive performance accuracy, older age, and the performance of a more demanding gait task. This last relationship is true for younger and older adults, but the impact on gait variability is even greater for older adults. The greater temporal variability observed during more demanding gait and cognitive tasks may have important implications for young and older adults ambulating in the community.

Disclosures: L.A. Zukowski: None. **P. Plummer:** None.

Poster

621. Memory and Cognition: Influence by Aging

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Topic: F.01. Human Cognition and Behavior

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1UL1RR031980-01

Title: Association between medial temporal lobe microstructure and cognitive function in healthy community-dwelling older adults

Authors: E. T. REAS[1], D. J. HAGLER, Jr.[1], N. S. WHITE[1], A. M. DALE[2], E. BARRETT-CONNOR[3], *L. K. MCEVOY[1];
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Abstract: The brain's medial temporal lobe is essential for declarative memory and undergoes structural alterations during the early stages of neurodegenerative memory disorders. Although memory decline is a common feature of typical aging, it remains unclear whether medial temporal lobe structural changes track cognitive function in normal aging, as they do under pathological conditions such as Alzheimer's disease and mild cognitive impairment. This study examined the association of medial temporal lobe microstructural organization and morphometry with cognitive function in healthy, community-dwelling older adults. Participants (N = 60; age range 60-99 years, mean 75 years; 63% women), with no history of neurological disorders or

stroke, completed a neuropsychological test battery and underwent structural magnetic resonance imaging (MRI) and diffusion weighted imaging. Regional cortical thickness and subcortical volume measures were extracted from MRI data using FreeSurfer software (www.FreeSurfer.net). Diffusion metrics for selected temporal lobe fiber tracks were derived using a probabilistic atlas of fiber tract locations and orientations (AtlasTrack; Hagler et al. Hum Brain Mapp. 2009;30:1535-1547). T1-weighted images were used to nonlinearly register the brain to a common space, and diffusion tensor orientation estimates were compared to the AtlasTrack atlas to obtain a map of the relative probability that a voxel belonged to a particular fiber given the location and similarity of diffusion orientations. These probability values were used to calculate weighted averages of the diffusion measures for each fiber tract. Results of FreeSurfer's automated brain segmentation were used to exclude voxels in fiber tract regions of interest that were primarily gray matter or CSF. After controlling for age, sex and education, lower global cognitive and memory scores correlated with reduced thickness in entorhinal and parahippocampal cortices and with altered microstructure in the fornix and parahippocampal cingulum. These findings suggest that even among healthy, community-dwelling older adults, microscopic and macroscopic changes in the medial temporal lobe may contribute to decline in cognitive function with age.

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Poster

621. Memory and Cognition: Influence by Aging

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Topic: F.01. Human Cognition and Behavior

Support: NIA 5R01AG044838-03

Title: Aging contributes to grey matter volume and attentional impulsivity correlates in frontoparietal functional connectivity

Authors: *J. J. CASTRELLON[1], L. C. DANG[1], S. F. PERKINS[1], G. R. SAMANEZ-LARKIN[2], D. H. ZALD[1];
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Abstract: Background: Attentional impulsivity (AI) is a trait marked by the inability to focus one's attention on a given task observed in psychopathology such as ADHD but prevalent in healthy individuals as well. The Barratt Impulsiveness Scale (BIS) assesses AI, motor impulsivity and nonplanning, and is among the most commonly used self-report measures of impulsivity. Given its role in attention, features of frontoparietal network (FPN) may be associated with age changes in AI. Past studies have suggested associations between grey matter volume (GMV) and functional connectivity (FC) in the FPN and impulsivity, although the studies have been limited to young (YA) and middle-aged (MA) samples, and have shown inconsistent relations. Little research address whether FC and GMV in the FPN are related to AI in the context of healthy aging. We aimed to determine whether FPN FC and GMV related to age and AI in a healthy adult sample. Method: Resting-state fMRI and T1-weighted structural images were acquired in 69 healthy adults (22-81). Independent component analysis (ICA) identified a FPN across all subjects. Dual regression analysis identified subject-specific temporal dynamics and linked spatial maps correlated with age and BIS, identifying relationships in the FC strength within a network. For follow-up analyses using voxelwise GMV as covariate, GMV values were derived from voxel-based morphometry. Results: Age and AI BIS were negatively correlated. FPN FC showed a positive correlation with age and a negative correlation with AI BIS. The age correlation remained after controlling for AI BIS. When controlling for age, however, the FPN FC relationship with AI BIS was lost. Remodeling the age effect with GMV as a covariate rendered it insignificant. A final analysis between GMV and FPN FC revealed a trending relationship. Conclusion: The findings demonstrate that decreasing AI and increasing age have overlapping correlates with FPN FC and that these associations were largely accounted for by age, but dependent on GMV effects. The GMV FPN FC trend further suggests that GMV may contribute to FPN FC. Together, the findings suggest that age may mediate AI and GMV changes in FPN FC, stressing the importance of age on attention networks.

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Poster

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Topic: F.01. Human Cognition and Behavior

Support: CONACYT 238826

UNAM DGAPA PAPIIT IG300115

Title: Neural connectivity during episodic memory formation in young and old adults

Authors: *S. CANSINO[1], C. ESTRADA-MANILLA[1], P. TREJO-MORALES[1], E. H. PASAYE-ALCARAZ[2], E. AGUILAR-CASTAÑEDA[3], P. SALGADO-LUJAMBIO[3], A. L. SOSA-ORTIZ[3];
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Abstract: Personal past events may be remembered along with the spatiotemporal context or source information present when we experienced the event or may be remembered without this information. The ability to retrieve contextual details is termed recollection, and it declines with advancing age, while the ability to remember the event without contextual information, known as familiarity, is only slightly affected in old age. Age effects on regional brain activations and deactivations have been identified during the encoding of information that will be remembered later through recollection or familiarity. However, how the interaction among these regions accounts for the decline of these two types of memories is still unknown. We used dynamic causal modeling (DCM) to analyze functional magnetic resonance imaging (fMRI) data. Neural connectivity during encoding of subsequent successful and unsuccessful spatial source memory retrieval was examined in young and old adults. DCM analyses were performed in brain regions that showed significant activity differences between age groups in the contrast between study items that were later recognized and assigned a correct source judgment with those whose sources were subsequently forgotten. Neural connectivity in the reverse contrast was also analyzed. Effective connectivity between the left medial orbitofrontal gyrus and left hippocampus was reduced in old adults relative to young adults during the encoding of subsequent source retrieval. The results suggest that age effects on recollection are not only due to local under-recruitment activity but also to less efficient interactions between brain regions.

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Poster

621. Memory and Cognition: Influence by Aging

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Topic: F.01. Human Cognition and Behavior

Support: CHOJU-IRYO-KENKYU

Title: Classification of age–related brain connectivity using resting state fMRI and the support vector machine

Authors: *T. IIDAKA[1], E. BAGARINAO[1], S. KOYAMA[2], M. KUNIMI[2], T. NAKAI[2]; [1]Nagoya University, Grad. Sch. of Med., Nagoya, Aichi, Japan; [2]Natl. Inst. for Geriatrics and Gerontology, Obu, Japan

Abstract: Age-related changes in brain function of healthy young and old subjects have been investigated with fMRI and cognitive tasks. Recently, functional connectivity analysis using fMRI in resting rather than task conditions has emerged as an important tool for understanding brain aging and dementia. A classification approach using machine learning such as the support vector machine (SVM) could therefore significantly contribute to this field of research. In the present study, we classified healthy young and old subjects' resting–state (rs–) fMRI activity by the SVM. We achieved high classification accuracy with relatively few features. Study participants included 53 young (mean age, 22.6 years, male/female, 25/28) and 57 old (mean age, 68.6 years, male/female, 24/33) healthy subjects. None of the subjects had cognitive impairment (MMSE > 24) or clinical depression. Whole brain echo planar images were obtained during the resting state with eyes open (3T, Siemens, Trio, TR = 3000 ms, TE = 30 ms, 64 × 64 matrix, 39 slices, 135 volumes). The images were preprocessed with SPM8. The mean signal time courses in 90 cerebral regions were then extracted with the Data Processing Assistant for Resting-State fMRI (DPARSF) software. A 90 × 90 correlation matrix of functional connectivity was created for each subject. The connectivity matrices were subjected to an in-house SVM program (linear SVM, C parameter = 1) that implemented principal component analysis and permutation tests to classify the groups. The results showed that the accuracy was 100% when using all subjects and 96.4% when subjects were split into training and test sets (10-fold cross validation). Of 4005 possible connections, high classification accuracy was obtained from only 66 pair-wise connectivities. The connected regions were mainly located in the frontal (29%), subcortical (23%), and temporal (20%) areas. A connectivity value between the anterior cingulate gyrus and olfactory gyrus in the left hemisphere significantly correlated with the age of old subjects ($r = –0.45$, $p < 0.05$, Bonferroni correction). Thus, we achieved high classification accuracy between the young and old subjects by using rs–fMRI and SVM. The age-related difference in connectivity was distributed across the whole brain; however, majority of the connectivities were in the frontal, subcortical, and temporal regions. In the future, the present study could be extended to develop a biomarker of aging and dementia by including subjects with cognitive impairment.

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Support: NIH/NIA R01 AG038465

Title: Integrity and selectivity of functional activation maps predict behavioral performance and successful aging

Authors: *C. G. HABECK, Y. GAZES, H. OH, Y. STERN;
Taub Inst., Columbia Univ., New York, NY

Abstract: For cognitive neuroimaging a self-evident idea postulates that similarity of cognitive processes implies corresponding similarity of neuroimaging substrates. A disruption of the relationship between similarity of cognitive processes and the corresponding similarity of neural substrates might signal “de-differentiation”, resulting in cognitive processes that are distinct sharing unduly similar activation maps. We operationalized a simple measure of such functional integrity and selectivity in two data sets: data set 1 contained 291 participants (age 20-77) who were imaged while performing 12 tasks, with 3 tasks for each of the following cognitive domains: episodic memory, fluid reasoning, perceptual speed, and vocabulary. The functional-integrity and selectivity measure is computed for each participant as the difference of the average Fisher-Z coefficient of the 12 possible WITHIN-domain task pairings vs. the average Fisher-Z coefficient of the 54 possible BETWEEN-domain pairings. Higher values in this measure were associated with better neurocognitive profiles, as it correlated negatively with age ($p=0.0036$), but positively with mean cortical volume ($p=0.0007$) and thickness ($p=0.0112$), years of education ($p=0.0022$), and verbal intelligence ($p=0.0180$). It also correlated positively with task performance in 10 of 12 tasks at $p<0.05$. A second data set contained 123 participants (age 20-70) performing a verbal Sternberg visual working-memory task with 3 memory loads in 3 task phases, yielding 9 task-activation maps per participant. The functional-integrity and selectivity measure was similarly computed as the difference of average Fisher-Z spatial correlation of activation maps WITHIN task phase (9 possible pairings) vs. BETWEEN task phases (27 possible pairings). While the measure did not correlate with age or years education, it positively correlated with verbal intelligence ($p=0.0023$), mean cortical volume ($p=0.0127$), neuropsychological measures of fluid reasoning ($p=0.0107$), perceptual speed ($p=0.0391$), vocabulary ability ($p=0.0055$). It also correlated negatively with the task reaction times in fMRI scanner ($p<0.01$ for all 3 memory-load conditions). Future research might assess to what extent

the functional-integrity and selectivity measure investigated in this report can provide diagnostic information about successful aging above and beyond structural brain measures and neuropsychological performance. The measure is computationally easy to implement, does not involve specially tailored group-level derivations and is particularly feasible for rich multi-task data sets.

Disclosures: C.G. Habeck: None. **Y. Gazes:** None. **H. Oh:** None. **Y. Stern:** None.

Poster

621. Memory and Cognition: Influence by Aging

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 621.13/X23

Topic: F.01. Human Cognition and Behavior

Title: Visual search performances does not predict age- related performance differences in an everyday memory task

Authors: *M. KEMPE[1,2], O. L. BOCK[1], D. MEMMERT[2];
[1]Inst. of Physiol. and Anat., [2]Inst. of Cognitive and Team/Racket Sport Res., German Sport Univ. Cologne, Cologne, Germany

Abstract: The age-related decline in memory tasks is well documented within the literature. However, it is still unclear how those results transfer into everyday life and what might impair memory performance of older adults in everyday life memory tasks. To explore age related differences, we used a shopping task to measure memory performance of sixteen younger (23.88 ± 4.15 years, 10 male) and sixteen older adults (71.19 ± 4.02 years, 12 male). Eye-movements were recorded to clarify if the reduced visual search performance of older adults is accountable for reduced memory performance. Older adults performed worse than younger adults in the everyday memory task. In line with previous findings, the age effect in the everyday memory task was more pronounced than in laboratory memory tasks. Further they showed a decrease in their visual search performance via increases in the number of fixations, number re-fixations and fixation time for target items. To check if impaired visual search and/or inhibition performance might be accountable for the age effect a linear regression analysis was conducted. Inhibition performance, but not visual search performance could predict the performance in the everyday memory task via the regression analysis. Therefore, we conclude that memory performance in everyday life might not be explained by the performance of searching for target items but by the performance to inhibit irrelevant visual information.

Disclosures: **M. Kempe:** None. **O.L. Bock:** None. **D. Memmert:** None.

Poster

621. Memory and Cognition: Influence by Aging

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 621.14/X24

Topic: F.01. Human Cognition and Behavior

Support: NIH/NIA R01 AG038465

Title: Life-time stability of reference ability neural networks

Authors: ***Y. STERN**, C. HABECK, Y. GAZES;
Cognitive Neurosience Division, Columbia Univ., New York, NY

Abstract: Analyses of large test batteries administered to individuals ranging from young to old have consistently yielded a set of latent variables representing reference abilities (RAs) that capture the majority of the variance in age-related cognitive change: Episodic Memory, Fluid Reasoning, Perceptual Processing Speed, and Vocabulary. The Reference Ability Neural Network Study administers 12 cognitive neuroimaging tasks (3 for each RA) to healthy adults age 20 -80 in order to derive unique neural networks underlying these 4 RAs and investigate how these networks may be affected by aging. We used a multivariate approach, linear indicator regression, to derive a unique covariance pattern or Reference Ability Neural Network (RANN) for each of the 4 RAs. RANNs were derived from the neural task data of 64 younger adults of age 30 and below. We then prospectively applied the RANNs to fMRI data from the remaining sample of 227 adults of age 31 and above in order to classify each subject-task map into one of the 4 possible reference domains. Overall classification accuracy across subjects was 0.82 ± 0.17. Classification accuracy by RA domain, was also very good; memory: 0.83 ± 0.25; reasoning: 0.89 ± 0.24; speed: 0.82 ± 0.30; vocabulary: 0.73 ± 0.35. Classification accuracy did not decline with age, suggesting that these networks remained intact throughout the age range. Higher mean brain volume was correlated with increased overall classification accuracy. Higher expression of any particular RANN was associated with the corresponding classification accuracy for that reference ability. Conversely, expression of a RANN for one domain was not associated with classification accuracy of any other domain. Despite the absence of behavioral performance in the derivation of these networks, expression of the fluid-reasoning network correlated with performance. While age did not influence the expression of the FLUID RANN in participants age 31 and above, this association declined with increasing age. These results provide support for the hypothesis that a set of specific, age-invariant neural networks underlies

these four RAs, and that these networks maintain their specificity with aging. The relationship between network expression and fluid reasoning performance was unexpected, since the RANNs were derived with no reference to task performance. Our eventual goal is to derive RANNS that are unique to each RA and whose expression correlates with the associated RA performance. We will then be in a position to evaluate how network expression or topographic composition may be affected by age-related brain changes in order to produce performance differences with aging.

Disclosures: Y. Stern: None. **C. Habeck:** None. **Y. Gazes:** None.

Poster

621. Memory and Cognition: Influence by Aging

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Program#/Poster#: 621.15/X25

Topic: F.01. Human Cognition and Behavior

Support: NIH/NIA R01 AG26158

Title: Unique white matter tract covariance patterns predict age-declining cognitive abilities

Authors: *Y. GAZES, Q. R. RAZLIGHI, D. O'SHEA, Y. STERN, C. G. HABECK;
Taub Inst., Columbia Univ., New York, NY

Abstract: Previous studies investigating the relationship of white matter integrity to cognitive abilities and aging and have either focused on a global measure or a few selected white matter tracts. Ideally, contribution from all of the white matter tracts should be evaluated at the same time. However, the high collinearity among white matter tracts precludes systematic examination of white matter tracts simultaneously without sacrificing power due to stringent multiple-comparison corrections. Multivariate covariance techniques enable comprehensive simultaneous examination of all white matter tracts without being penalized for high collinearity among observations. Method: In this study, Scaled Subprofile Modeling (SSM) was applied to the mean integrity of 18 major white matter tracts to extract covariance patterns that optimally predicted four cognitive abilities (perceptual speed, episodic memory, fluid reasoning, and vocabulary) in 346 participants across ages 20 to 79 years old. Using expression of the covariance patterns, both age by white matter interaction and mediation of white matter integrity on age-related differences in cognition were tested separately, but inferences from the mediation analyses were cautiously made given cross-sectional data set was used in the analysis. Results: A covariance pattern was identified that significantly predicted all cognitive abilities except vocabulary. Age by white matter pattern interactions were not significant for any of the three abilities. The

expression of the corresponding white matter pattern accounted for a significant portion of the variability in each of the three abilities after partialling for age. Furthermore, each of the patterns mediated the effect of age on the respective cognitive ability. A distinct set of white matter tracts was most influential in each of the three patterns. The white matter pattern accounting for fluid reasoning showed the most number of influential white matter tracts whereas the episodic memory pattern showed the least number. Conclusion: Specific patterns of white matter tracts make significant contributions to the age-related differences in perceptual speed, episodic memory, and fluid reasoning but not vocabulary. Other measures of brain health will need to be explored to reveal the major influences on the vocabulary ability.

Disclosures: Y. Gazes: None. **Q.R. Razlighi:** None. **D. O'Shea:** None. **Y. Stern:** None. **C.G. Habeck:** None.

Poster

621. Memory and Cognition: Influence by Aging

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Program#/Poster#: 621.16/X26

Topic: F.01. Human Cognition and Behavior

Support: NIA AG025526

State of Arizona DHS

Title: Relation of white matter hyperintensity volume to cognitive performance in older adults

Authors: *L. A. NGUYEN[1,6,7], P. K. BHARADWAJ[1,6,7], K. A. HAWS[1,6,7], M. C. FITZHUGH[1,6,7], T. P. TROUARD[2], G. A. HISHAW[3], G. E. ALEXANDER[1,6,7,4,5]; [1]Dept. of Psychology, Univ. of Arizona, Tucson, AZ; [2]Biomed. Engin., Univ. of Arizona, University of Arizona, AZ; [3]Univ. of Arizona, Department of Neurology, AZ; [4]Physiological Sci. Grad. Interdisciplinary Program, [5]Neurosci. Grad. Interdisciplinary Program, Univ. of Arizona, Tucson, AZ; [6]Evelyn F. McKnight Brain Inst., Tucson, AZ; [7]Arizona Alzheimer's Consortium, Phoenix, AZ

Abstract: Greater prevalence of cerebral white matter abnormalities, which appear as hyperintense regions in T2 FLAIR magnetic resonance imaging (MRI) scans, have been associated with increasing age, diminished cognitive performance, and cardiovascular risk factors, such as hypertension. We investigated the relation between white matter hyperintensity (WMH) volume and cognitive performance in a group of community-dwelling, elderly adults

with and without histories of hypertension to further evaluate the role of WMH in cognitive aging. A sample of 74 neurologically healthy older adults, 75-89 years of age, with treated hypertension (N = 32) and without hypertension diagnosis or treatment (N = 42) completed a battery of neuropsychological tests. T1-weighted volumetric and T2 FLAIR MRI scans were acquired on a 3T GE Signa Excite scanner. The volumes of WMHs were computed with a multispectral, automated lesion segmentation method to produce probability maps using Statistical Parametric Mapping (SPM8) and a lesion segmentation toolbox (LST; Schmidt et al., 2012). The results indicated that greater WMH volume was related to poorer performance ($0.001 \leq p \leq 0.018$) on several measures of memory (Selective Reminding Test: Sum Recall, Long-Term Storage, Long-Term Retrieval, and 30-minute Delayed Recall), executive functions (Paced Auditory Serial Addition Test, Trail Making Test - part B, and Wisconsin Card Sorting Test categories completed), and visuo/psycho-motor processing speed (Trail Making Test - part A and Grooved Pegboard), but was not related to performance on general measures of intellectual function (Wechsler Adult Intelligence Scale-IV - Full Scale IQ). After individually controlling for age ($0.006 \leq p \leq 0.049$) and the combination of age and hypertension status ($0.007 \leq p \leq 0.048$) in the cohort, these specific associations with cognitive performance remained significant. In a sample of generally healthy, community-dwelling older adults, having greater WMH volume is associated with poorer memory, executive functions, and processing speed, even after controlling for age and hypertension status. Together these findings suggest that WMH volume may be an important factor contributing to the individual differences observed in cognitive aging. Further research is needed to evaluate the longitudinal impact of white matter lesion volumes on cognitive decline in the context of healthy aging.

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Poster

621. Memory and Cognition: Influence by Aging

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Topic: F.01. Human Cognition and Behavior

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Heart and Stroke Foundation of Canada (HSFC) (Grant number 13-0001867)

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Title: Association between lifetime physical activity and cognitive functioning in older community dwelling adults

Authors: *S. J. GILL[1,2,12], C. M. FRIEDENREICH[3,13,4], T. T. SAJOBI[3,12,5], S. R. LONGMAN[6,14,12], L. L. DROGOS[12,7], M. H. DAVENPORT[12,7], A. V. TYNDALL[12,7], G. A. ESKES[7,15], D. B. HOGAN[12,3,5,8], M. D. HILL[12,3,5], J. S. PARBOOSINGH[9,10], B. J. WILSON[8], M. J. POULIN[12,5,7,16,11];
[2]Med. Sci., [3]Community Hlth. Sci., [4]Oncology, [5]Clin. Neurosci., [6]Psychology, [7]Physiol. & Pharmacol., [8]Med., [9]Med. Genet., [10]14Alberta Children's Hosp. Res. Inst. for Child and Maternal Hlth., [11]Fac. of Kinesiology, [1]Univ. of Calgary, Calgary, AB, Canada; [12]Hotchkiss Brain Inst., Calgary, AB, Canada; [13]Cancer Epidemiology and Prevention Res., [14]Rehabil. Psychology, Alberta Hlth. Services, Calgary, AB, Canada; [15]Psychiatry, Psychology & Neurosci., Dalhousie Univ., Halifax, NS, Canada; [16]15Libin Cardiovasc. Inst. of Alberta, Calgary, AB, Canada

Abstract: Worldwide nearly 44 million people currently live with Alzheimer's disease or related dementias. Before the signs and symptoms of dementias are seen, older adults may have a decrease in their cognitive abilities or cerebrovascular functioning. To prevent these pre-clinical symptoms modifiable lifestyle factors such as physical activity (PA) must be studied to determine how to attenuate or improve brain health. The aim of this cross-sectional study is to determine if total lifetime PA is associated with better cognitive functioning with aging and if cerebrovascular function mediates this association in a sample of 226 (118 females, 52.2%) community dwelling older adults aged 55-90 years (66.5±6.4 years) in the *Brain in Motion* Study. Each participant completed the Lifetime Total Physical Activity Questionnaire, a neurophysiological assessment and a non-invasive cerebral blood flow velocity test of the middle cerebral artery. Multiple robust linear regressions were used to model the associations between lifetime PA and global cognition after adjusting for age, sex, North American Adult Reading Test results (i.e. estimated IQ), maximal aerobic capacity, body mass index and interaction terms (age, sex, lifetime physical activity). Mediation analysis was used to assess the effect of cerebrovascular measures on the association between lifetime physical activity and global cognition. Post-hoc analyses were performed assessing past year physical activity and current fitness levels (maximal aerobic capacity) relation to global cognition and cerebrovascular measures. Better global cognitive performance was associated with higher lifetime PA ($p=0.03$), recreational PA ($p=0.018$), vigorous intensity PA ($p=0.013$), PA between the ages of 0 and 20 years ($p=0.028$), between the ages of 21 and 35 years ($p<0.0001$) and for past year PA ($p=0.0.19$). Cerebrovascular measures did not mediate the association between PA and global

cognition scores ($p>0.5$). Cerebrovascular measures partially mediated the relation between current fitness (O_2max) and global cognition. This study revealed statistically significant associations between higher levels of PA (i.e., total lifetime, recreational, vigorous and past year) and improved cognitive function in later life that did not appear to be mediated by cerebrovascular function. Current fitness levels were also associated with global cognition and these relations were partially mediated by measures of cerebrovascular health.

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Poster

621. Memory and Cognition: Influence by Aging

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Topic: F.01. Human Cognition and Behavior

Support: NIH Grant AG034570

NIH Grant AG049564

Title: Contributions of age and Alzheimer's pathology to hippocampal memory network function in healthy elderly

Authors: *S. M. MARKS[1], S. N. LOCKHART[1], K. L. ARNEMANN[1], J. W. VOGEL[1], H. D. SCHWIMMER[1], W. J. JAGUST[1,2];
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Abstract: As part of a larger neural network, the hippocampus is central to successful memory processes and relies on pattern separation to orthogonalize similar events. Memory deficits are often the first indicator of cognitive decline with respect to Alzheimer's disease (AD) and there is reason to believe that AD pathology uniquely impacts the memory network beyond changes that occur with normal aging. The aim of this study was to investigate the impact of AD pathology on hippocampal function and its associated network during episodic memory. Thirty-seven cognitively normal elderly and 14 young controls participated in a functional MRI paradigm designed to emphasize pattern separation. A subset of elderly participants underwent

Pittsburgh Compound B and AV-1451 PET scans to measure beta-amyloid (Aβ) and tau neurofibrillary tangles, as well as structural, diffusion and resting-state MRI. Aβ was quantified globally and locally in the retrosplenial cortex (RSC). Tau was quantified locally in the entorhinal cortex. Connectivity of posterior parietal regions and medial temporal lobes (MTL) was assessed using seed-based correlation of RSC and parahippocampal resting-state time series, in addition to average cingulum fractional anisotropy (FA). Manually segmented hippocampal subfield ROIs were used to measure task activation and volume. Older adults performed worse on the memory task ($F = 28.4$, $p < 0.001$) and showed increased activation in right dentate gyrus/CA3 (DGCA3) compared to young controls ($F = 5.3$, $p = 0.026$), confirming previously published reports. Increased DGCA3 activity was associated with worse performance at trend levels ($t = -1.8$, $p = 0.076$). Additionally, larger hippocampal volumes predicted better performance in older adults ($t = 2.1$, $p = 0.046$). Average cingulum FA was associated with DGCA3 activity ($t = -2.1$, $p = 0.052$), suggesting that worse performance may result from inefficient network communication. AD biomarkers had no direct relation with task performance or activation, but did influence local structure and connectivity. Specifically, RSC Aβ was associated with reduced connectivity between RSC and parahippocampus ($t = -2.5$, $p = 0.023$); and, tau in entorhinal cortex was marginally associated with DGCA3 volume ($t = -1.9$, $p = 0.075$). These preliminary results suggest that in addition to age-related changes, AD pathology may influence memory in two distinct ways. First, MTL tau accumulation leads to focal neurodegeneration, altering the structure of the hippocampus. Second, Aβ alters long-range communication within the network, inhibiting efficient information flow to the hippocampus. Further work needs to be done to confirm these findings.

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Poster

621. Memory and Cognition: Influence by Aging

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Topic: F.01. Human Cognition and Behavior

Support: Marie Curie FP7 Grant

Title: Transcranial direct current stimulation over the right prefrontal cortex leads to time-dependent enhancement of sustained attention in ageing

Authors: *M. BROSNAN[1], M. ARVANEH[2], P. M. DOCKREE[2], I. ROBERTSON[2];
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[2]Trinity Col. Inst. of Neurosci. and Sch. of Psychology, Dublin, Ireland

Abstract: Sustained attention can be described as maintaining a goal-directed focus in the face repetitive nonarousing tasks. The right dorsolateral prefrontal cortex appears to play a crucial role at endogenously maintaining attentional focus. Here we explored the potential of transcranial Direct Current Stimulation (tDCS) over the right prefrontal cortex to enhance sustained attention in an ageing population. Cognitively healthy older adults (aged 64-84) received tDCS while performing a sustained attention task, the Sustained Attention to Response Task (SART). A tDCS-induced reduction in RT variability was observed during real stimulation, exclusively during the first half of stimulation. RT variability on the SART is a sensitive measure of fluctuations in sustained attention, as the high frequency of response requirements allow an almost constant monitoring of attention. This time-dependent enhancement of sustained attention during stimulation may be suggestive of a 'homeostatic-like' response to tDCS over the prefrontal cortex. Analysis of spectral electroencephalogram (EEG) and event related potentials (ERPs) recorded during stimulation is currently underway.

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Poster

621. Memory and Cognition: Influence by Aging

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Topic: F.01. Human Cognition and Behavior

Support: NIA 1R01AG048076

McKnight Foundation Independent Research Grant

Title: Medial temporal lobe representational pattern similarity during encoding predicts episodic memory performance among healthy older adults

Authors: *V. A. CARR[1], A. M. KHAZENZON[1], J. D. BERNSTEIN[1], C. P. LITOVSKY[1], G. A. KERCHNER[2], A. D. WAGNER[1];
[1]Psychology, [2]Neurol. and Neurolog. Sci., Stanford Univ., Stanford, CA

Abstract: Healthy aging is often accompanied by impairments in episodic memory - memory for events in our daily lives. Individuals differ in the degree to which they experience such impairments, and the underlying factors contributing to this variability remain unclear. Computational models posit that age-related memory impairments are related to synaptic loss and weakening among perforant path inputs to the hippocampus, a region known to play a key role in episodic memory. These models suggest that such age-related changes reduce the capacity of the hippocampus to engage in pattern separation, a process allowing for the encoding of separable memory representations. As a result of impaired pattern separation, the retrieval of details specific to a given learning episode will also be impaired, leading to deficits in episodic memory. Emerging univariate fMRI findings provide initial support for this notion, demonstrating that impairments in item memory in healthy older adults are associated with dysfunction in hippocampal subfield DG/CA3, a region known to play a key role in pattern separation. Here, we extend these findings in two ways. First, given the importance of the hippocampus in forming associations between features of an event, we evaluated hippocampal subfield function in healthy older adults using high-resolution fMRI as they performed an associative memory task. Second, using representational pattern similarity analyses, we evaluated the degree to which trial-specific patterns of encoding activity were dissimilar or similar to one another, indicating a bias towards separation or generalization, respectively. Linear regression analyses revealed that measures of encoding pattern similarity were predictive of subsequent memory performance. Such results provide novel evidence that age-related alterations in hippocampal computations during encoding contribute to impairments in episodic memory.

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Poster

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Topic: F.01. Human Cognition and Behavior

Support: NIA 1R01AG048076

McKnight Endowment Fund Memory and Cognitive Disorders Award

Dana Foundation

Title: Structural and functional hippocampal changes underlying age-related memory retrieval impairment

Authors: *A. M. KHAZENZON, V. A. CARR, J. D. BERNSTEIN, C. P. LITOVSKY, G. A. KERCHNER, A. D. WAGNER;
Stanford Univ., Stanford, CA

Abstract: Healthy older adults frequently perform worse on tests of episodic memory relative to younger adults, even in the absence of memory complaints. The neural mechanisms underlying such age-related memory decline remain underspecified, though extant evidence highlights the potential contributions of medial temporal lobe changes with age. Hippocampal circuit function is critical for episodic retrieval. Computational models and initial data suggest that, when presented with a partial cue for an episode, the hippocampus performs pattern completion to retrieve associated elements. This hippocampal completion process is further thought to drive activity in neocortex, where event features are reinstated. Selective atrophy and functional changes in hippocampal subfields that affect pattern completion processes might therefore contribute to age-related episodic retrieval impairment. Here, we examined whether focal changes in hippocampal subfield structural integrity (measured using 7T MRI) along with functional alterations (measured using 3T high-resolution fMRI) contribute to age-related changes in associative memory. We evaluated both univariate measures of hippocampal subfield activity as well as multivariate measures of ventral occipitotemporal activity to determine whether individual differences in associative memory performance can be explained by differences in hippocampal pattern completion-mediated cortical reinstatement. Initial analyses suggest that performance during an associative memory task can be successfully predicted by these functional measures along with measures of hippocampal subfield thickness, providing support for the notion that age-related changes in hippocampal computations contribute to age-related memory decline. Funding: NIA 1R01AG048076, McKnight Endowment Fund Memory and Cognitive Disorders Award, Dana Foundation

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Poster

621. Memory and Cognition: Influence by Aging

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Topic: F.01. Human Cognition and Behavior

Support: MEXT/JSPS KAKENHI Grant Number 25245068 and 14J11049

Title: A deficit-compensation brain activation pattern common to working memory and functional mobility in older adults

Authors: ***T. KAWAGOE**[1], M. SUZUKI[1], S. NISHIGUCHI[2], N. ABE[3], Y. OTSUKA[3], R. NAKAI[3], M. YAMADA[4], S. YOSHIKAWA[3], K. SEKIYAMA[1];
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Abstract: Functional mobility and cognitive function often declines with age. We previously found that functional mobility measured by Timed Up and Go Test (TUG) is associated with cognitive performance for visually-encoded (i.e. for location and face) working memory (WM) in older adults. It suggests a common neural basis between TUG and visual WM. To elucidate this relationship further, the present study aimed to examine the neural basis for the WM-mobility association. According to one of the well-known neural compensation models in aging, we hypothesized that "attentional" brain activation for easy WM would increase for participants with lower mobility. The data from 32 community dwelling healthy older adults (MMSE > 26) were analyzed, which include brain activation during easy WM tasks via functional Magnetic Resonance Imaging (fMRI) and mobility performances via both TUG and a simple walking test. WM performance was significantly correlated with TUG but not with simple walking. Some prefrontal brain activities during WM were negatively correlated with TUG performance while positive correlations were found in internal structures including thalamus, putamen, and cerebellum. Moreover, the activation of "automatic" internal regions was significantly correlated with WM performance, with less activation for lower WM performers.These results indicate that older adults with lower functional mobility used more "attentional" and less "automatic" resources for easy WM tasks. To date, the frontal compensation has been proposed separately in motor and cognitive domain, which was assumed to compensate for deficit of other brain areas, however such deficit (deactivation) was less clear in the previous studies.The present study observed such deactivation associated with lower functional performance, which was found in "automatic" regions. We conclude that a common deficit-compensation activation pattern is likely the neural basis for the association between visual WM and functional mobility.

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Poster

621. Memory and Cognition: Influence by Aging

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Topic: F.01. Human Cognition and Behavior

Support: NIH Grant K01-AG028774

NIH Grant F32-AG049574

Title: The role of medial temporal lobe regions in incidental and intentional retrieval of relational and item information in aging

Authors: *W.-C. WANG[1], K. S. GIOVANELLO[2];
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Abstract: Considerable neuropsychological and neuroimaging work indicates that the medial temporal lobes are critical for both item memory and relational memory retrieval. However, there remain outstanding issues in the literature, namely the extent to which medial temporal lobe regions are differentially recruited during incidental and intentional retrieval of relational and item information, and the extent to which aging may affect these neural substrates. The current fMRI study sought to address these questions; participants incidentally encoded word pairs embedded in sentences and incidental item and relational retrieval was assessed through speeded reading of intact, rearranged, and novel word-pair sentences, while intentional item and relational retrieval was assessed through old/new associative recognition of intact, rearranged, and novel word pairs. Results indicated that, in both younger and older adults, anterior hippocampus and perirhinal cortex support incidental and intentional item retrieval, but parahippocampal cortex differentially supports these two forms of item retrieval. In contrast, posterior hippocampus supports incidental and intentional relational retrieval in both age groups and an adjacent cluster in posterior hippocampus was recruited during both forms of relational retrieval for older but not younger adults. Our findings suggest that there are both shared and distinct roles for medial temporal lobe regions in incidental and intentional retrieval of item and relational information, and further indicate that these regions may, under certain conditions, be overrecruited in healthy aging.

Disclosures: W. Wang: None. **K.S. Giovanello:** None.

Poster

621. Memory and Cognition: Influence by Aging

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 621.24/X34

Topic: F.01. Human Cognition and Behavior

Support: CIHR Grant MOP126105

Alzheimer's Society of Canada Grant 1435

Title: Investigating linear and nonlinear age-related changes in the functional neural correlates of context memory across the adult lifespan

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Abstract: In healthy aging, larger reductions in context or source memory relative to item memory have consistently been found. Previous functional neuroimaging studies have revealed age-group differences in the prefrontal (PFC) and posterior regions supporting context memory in older vs. younger adults. More recently, studies have found that differential activation in PFC regions associated with context memory arises as early as midlife. However, little is known about the trajectory of functional brain changes across the adult lifespan that contribute to context memory decline with age. It is possible that some functional brain changes across the adult lifespan are linear and others nonlinear. The current study used functional magnetic resonance imaging (fMRI) to investigate linear and residualized quadratic (parabolic) changes in context memory networks across young (ages 20-35), middle-aged (ages 40-58) and older (ages 60-76) adults. Two context memory tasks tested for the spatial and temporal information of faces, and participants completed an easy and difficult version of each task in order to help characterize performance effects vs. age effects. Behaviorally, a Task (spatial, temporal) x Difficulty (easy, difficult) x Group (young, middle-aged, older) ANOVA revealed that, across tasks, young adults outperformed both middle-aged and older adults and that middle-aged adults performed no differently from older adults ($p<.05$). Using a multivariate behavioral partial least squares (B-PLS) approach, our fMRI results identified a whole-brain network of regions showing linear increases and decreases in activation with age, as well as a network of regions showing increases and decreases in activation specific to midlife relative to young and older adulthood. Our results suggest that some network regions may differentially contribute to context memory across the adult lifespan.

Disclosures: E. Ankudowich: None. **S. Pasvanis:** None. **M.N. Rajah:** None.

Poster

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Topic: F.01. Human Cognition and Behavior

Support: NIH Grant R37AG024102

NIH Grant F32AG042228

Title: Factors modifying longitudinal change in white matter tract integrity in healthy midlife and older adults

Authors: *A. BILLIG[1], K. M. KENNEDY[2], P. R. A. W. ROBINSON[3], K. SCHAIE[4], S. L. WILLIS[4];
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Abstract: Studies examining longitudinal change in white matter (WM) tracts are limited, particularly those including modifiers of change. We examined 4-year change in white matter tract diffusivity over 3 occasions in participants of the Seattle Longitudinal Study: N = 212; Mean Age=69 at first scan, Range=56-91, SD=7.71; Mean education: 16 yr; Male: 43%, Female=57%. Tract data were processed with FSL software (eddy correction, skull stripping, tensor computation). Probtrackx was used for probabilistic fiber tracking in native diffusion space using starting and wayfinding seeds for each tract of interest. Fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) were measured in 5 tracts: superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), uncinate fasciculus (UNC), fornix (FNX) and cingulum (CING). Multivariate multilevel models using a stepwise modeling procedure estimated longitudinal change. A baseline model of change in the aforementioned tracts was used to predict cross-sectional age differences (AGE) and individual differences in rate of change (TIME) in WM integrity. This model was followed by the introduction of explanatory variables (APOE genotype, Hypertension (HBP), Education (EDUC), and Sex). Significant ($p < .05$) longitudinal TIME effects were found for: AD(SLF, UNC); RD(ILF). AGE had a significant effect on the mean FA along the ILF, UNC, CING, FNX tracts ($p<0.001$). A significant Sex by TIME interaction was found only for RD in UNC, with the females showing a steeper increase in slope than the males. Significant gender differences were found for FA in the CING ($p<0.01$) and FNX ($p<.05$) tracts with higher FA for males. No significant effects for APOE were found, though an effect of HBP on FA in SLF was discovered ($p <0.05$). A significant effect of education occurred on FA in the FNX ($p<0.05$). These findings indicate that axial and radial diffusivities along these tracts are mostly affected by TIME with Sex as a

modifier, while fractional anisotropy is affected by AGE with Sex, Hypertension, and Education as modifiers.

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Poster

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Topic: F.01. Human Cognition and Behavior

Support: NIA Grant R01-AG034578-01

Title: Neural correlates of loneliness in younger and older adults

Authors: *A. D'AGOSTINO, T. CANLI;
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Abstract: Loneliness, defined as the subjective experience of social isolation, has been linked to poor health outcomes including depression and cardiovascular disease. To improve upon current treatments, the interaction between genetic and environmental risk factors for loneliness and their effect on the brain must be better understood. The current study investigated the brain basis of loneliness in both younger (mean age = 20.35) and older adults (mean age = 62.88). We used functional magnetic resonance imaging (fMRI) and an emotional valence picture task to address this question. FMRI data were collected on a 3T Siemens Trio Scanner, with functional whole-brain images acquired using a gradient echo T2*-weighted EPI scan (TR=2.5 s; TE=30 ms; flip angle=90; FOV=256mm). 100 subjects (49 older, 51 younger) viewed positive and negative social and non-social images in the scanner followed by completion of questionnaires including an objective measure of loneliness, the Social Network Index, and a subjective measure of loneliness, the UCLA loneliness scale. Saliva samples were collected from all subjects for genotyping analysis of single nucleotide polymorphisms (SNPs) in two genes of interest (*OXTR* and *AVPR1A*). Questionnaire results indicated that compared to younger adults, older adults were significantly less lonely, trait anxious, shy and emotionally suppressive. Furthermore, fMRI results indicated that older adults showed significantly less activation in the precentral gyrus (BA6), inferior parietal lobe and precuneus during viewing of negative social images compared to fixation ($p< 0.05$, FWE corrected). Gender differences were also seen in response to viewing of negative social images compared to negative non-social images, with females showing

significantly greater activation in the cingulate gyrus ($p < 0.05$, FWE corrected). Finally, genetic analyses demonstrated that across all subjects, those with the G/G genotype for the rs53576 SNP of the oxytocin receptor gene (*OXTR*) scored significantly lower on the shyness scale compared to the A/G genotype ($p < 0.005$). The present findings indicate age, gender and genetic differences in social and emotional processing. In addition to the results presented here, functional connectivity analyses will be performed to explore whether putative neural circuits of social behaviors show different patterns of connectivity in lonely and non-lonely adults.

Disclosures: **A. D'Agostino:** None. **T. Canli:** None.

Poster

621. Memory and Cognition: Influence by Aging

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Program#/Poster#: 621.27/X37

Topic: F.01. Human Cognition and Behavior

Support: Evelyn F. McKnight Brain Institute

Arizona Alzheimer's Consortium

Title: Age-related differences in networks of brain activation across two executive functioning domains - updating and task-switching

Authors: *K. KAWA[1,2], M. B. SCHMIT[2], J. A. CARDOZA[2], A. M. STICKEL[2], E. L. GLISKY[2], L. RYAN[2];
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Abstract: Introduction. Miyake et al. (2000), using factor analysis, identified three relatively independent, yet related executive function processes. These included: 1) shifting between multiple tasks or mental sets, 2) updating and monitoring information in working memory, and 3) inhibition of prepotent or dominant responses elicited by a task. While previous studies have investigated the age-related differences in neural mechanisms underlying a single measure of executive functioning such as task-switching (Madden et al., 2010), fewer studies have investigated the mechanisms underlying age-related differences on multiple measures of executive functions in the same individuals. Methods. Older adults (n = 20; 60-79 years) and younger adults (n = 11; 18-31 years) were tested on two fMRI paradigms measuring updating and shifting. In the running span (updating) paradigm, the participants were presented with series of numbers and asked to continually remember the last three numbers. The length of the series of

numbers ranged from 3 to 5 to 7 in order to test task difficulty. In the task-switching paradigm (shifting), participants were presented with letters of the alphabet in either a square shape or diamond shape. If the letter was presented in a square, they responded whether the letter was printed in upper case or lower case. If the letter was presented in a diamond, they responded whether the letter was a consonant or a vowel. Results. In the running span paradigm, we observed a similar network of activation between older and younger adults. However, with increasing task difficulty, the older adults showed a greater extent of activation than the younger adults in this network, particularly in the right middle temporal gyrus, right inferior parietal lobule, and the middle frontal gyrus bilaterally. In contrast, during task-switching the two groups showed different networks of activation. The younger adults engaged greater frontal, parietal, and basal ganglia regions, while older adults engaged lateral frontal and visual cortices. Conclusion. Our results suggest that older and younger adults recruit similar or distinct networks of activation dependent upon the type of executive functioning task being performed. The differential recruitment highlights the importance of examining multiple executive functions within the same cohort to gain a greater understanding of the neural mechanisms underlying executive functioning and how these mechanisms change with age.

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Poster

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Location: Hall A

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Program#/Poster#: 621.28/X38

Topic: F.01. Human Cognition and Behavior

Support: CNPq

Title: Dietary zinc serum levels: preventing memory decline and depression in late adulthood

Authors: *A. A. OLIVEIRA, JR[1], T. JACOBSEN[2], T. FONSECA[3], M. FIEGENBAUM[2], F. ANDRADE[4];
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Abstract: The micronutrient Zinc is an essential molecular marker for several neurobiological functions. Its deficiency may affect neurogenesis, increase neuronal apoptosis and represent a

risk factor for the development of several neuropsychiatric disorders. Recent reports have suggested that a zinc diet treatment could significantly improve memory performance and reduce depression. Memory impairment and depression are among the most frequent complaints during aging. The progressive natural decline of memory produces lesser problems than more serious conditions observed on late adulthood. It is, however, a condition that worries most of the elderly population. Although widely studied as a psychopathology, depression is a pathological condition in increasing need of attention on aging with less biological comprehensive information available. There are unclear relationships between dietary zinc, memory deficits and depression. They share however a strong link with aging. In this study, we investigate the zinc serum levels and its relationship with depression and memory decline in late adulthood. For this purpose, 200 individuals over 50 years of age were evaluated for depression and memory. From these subjects, 16 indicated depression and were matched to 16 individuals without depression. All participants were examined regarding their zinc serum levels. Finally, the relationships between depression and memory deficits were analyzed. The results suggested that dietary zinc serum levels have a role important role preventing deficits such as memory impairment and depression.

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Poster

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 621.29/X39

Topic: F.01. Human Cognition and Behavior

Title: The effects of Omega-3 fatty acid supplementation on cognitive abilities in healthy adults

Authors: *D. LEHMAN, G. LECKIE, K. ERICKSON, S. SEREIKA, D. KUAN, S. MANUCK, M. MULDOON;
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Abstract: Long-chain, omega-3 fatty acids (LCn-3FAs) have several important biochemical roles in the brain, including modulation of synaptic plasticity. Mammals fed diets deficient in LCn-3FAs have behavioral abnormalities and reduced neuronal growth and synaptic proliferation. Western diets contain a median of just 100 mg/day of LCn-3FAs, and observational studies link low consumption with decrements in cognitive performance. To test for a causal relationship in humans, we conducted a randomized and double-blind clinical trial in

mid-life adults 30-55 years of age. Subjects were 271 adults (118 men, 153 women) consuming no more than 300 mg/day of LCn-3FAs. Each was randomized to 17 weeks of supplementation with 1400 mg/day of LCn-3FAs as fish oil (n = 134) or placebo capsules containing 1400 mg/day of soybean oil (n = 137). A neuropsychological test battery was completed at baseline and at study completion. Outcome measures included 11 cognitive tests categorized into domains such as fluid intelligence (Matrix reasoning, Block Design) and psychomotor speed (Stroop Word Time, Trails A Time). At baseline, there were no significant group differences in gender, age, education or IQ. Participant blinding was verified, and capsule adherence was over 90% in both groups. Effects of supplementation on multiple cognitive domains, relative to baseline performance and adjusted for placebo-effects, will be reported. Differences in any cognitive domain in favor of the treatment group at follow-up would constitute strong evidence that LCn-3FA consumption affects cognitive functioning during middle-adulthood and potentially impacts risk for cognitive impairment with aging.

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Poster

621. Memory and Cognition: Influence by Aging

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Topic: F.01. Human Cognition and Behavior

Support: Abbott Nutrition, Research Grant

University of Georgia Bio-Imaging Research Center, Administrative Support

Title: Lutein and zeaxanthin are related to neurobiological efficiency during cognitive performance: An fMRI study

Authors: *C. A. LINDBERGH, D. TERRY, C. MEWBORN, M. BELLO, E. BOVIER, L. M. RENZI, B. R. HAMMOND, L. MILLER;
Univ. of Georgia, Athens, GA

Abstract: Objective: While historically studied in relation to eye health, an emerging literature suggests that lutein (L) and zeaxanthin (Z) may benefit cognitive functioning, possibly through antioxidant and anti-inflammatory effects. The present study sought to evaluate the mechanisms by which L and Z impact cognition using functional magnetic resonance imaging (fMRI). It was

hypothesized that greater levels of L and Z would predict increased neurobiological efficiency (i.e., reduced activation) in older adults during learning and memory performance. **Methods**: 43 community-dwelling older adults (64-86 years) participated in an fMRI-adapted verbal learning task that involved learning pairs of unrelated words (mean age = 71.55, mean education = 16.66 years, 58% female, 100% Caucasian). The paradigm was comprised of several repetitions of learning trials and recall trials interspersed with distractor trials. L and Z levels were measured via two standard, validated procedures: blood serum concentrations and macular pigment optical density (MPOD). FMRI data were processed in SPM12 using the distractor trials as the imaging contrast for learning and recall trials ($p < 0.05$, family-wise error corrected, minimum voxel cluster = 8). L and Z serum concentrations and MPOD values were then entered, separately, as covariates in regression-based analyses of blood-oxygen-level-dependent (BOLD) signal. **Results**: L and Z measures were not significantly related to behavioral measures of verbal memory performance ($p > 0.05$). However, fMRI covariate analyses revealed that L and Z serum concentrations were negatively related to BOLD activation during learning and memory processes in several relevant brain regions, including left central and left parietal operculum cortex, left superior parietal lobule, left postcentral gyrus, left precentral gyrus, and lateral occipital cortex bilaterally ($p < 0.01$). Greater MPOD significantly predicted attenuated BOLD signal in left insular cortex, left inferior frontal gyrus, left supramarginal gyrus, left planum polare, left cerebellar regions, right middle temporal gyrus, right middle frontal gyrus, and occipital pole bilaterally ($p < 0.01$). **Conclusions**: To our knowledge, this is among the first attempts to shed light onto the neural mechanisms underlying the relationship of L and Z to cognition in humans. Results suggest that dietary intake may improve brain efficiency during memory encoding and retrieval by promoting more honed neural networks and reducing need for compensatory recruitment in regions commonly associated with age-related deterioration.

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Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: F.01. Human Cognition and Behavior

Support: NIH

CIHR

OGS

Title: Attentional regulation training is associated with flexible engagement of frontal control and default brain networks in older adults

Authors: *A. ADNAN[1], G. R. TURNER[2], A. CHEN[3], T. NOVAKOVIC-AGOPIAN[3], M. D'ESPOSITO[4];
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Abstract: The ability to attend to relevant information and filter out distracting information is crucial for goal-directed cognition (GDC). Older adults show pronounced deficits in this ability. Neuroimaging evidence suggests that this might arise from an age-related decline in top-down modulatory influences from prefrontal cortices to posterior perceptual regions (e.g. visual association cortices). There is evidence that young adults flexibly recruit frontal-parietal control network (FPN) and default network (DN) brain regions to enhance and suppress goal-relevant and irrelevant information respectively. We recently demonstrated that attentional regulation training leads to enhanced functional engagement of fronto-parietal and dorsal attention regions during GDC. Here we implement an event-related fMRI analysis to investigate whether improved GDC post-training is associated with flexible engagement of FPN and DMN. Specifically, we asked whether training was associated with (i) FPN activation during enhancement of relevant information and (ii) DN activation during suppression of irrelevant information. Healthy older adults were randomized to a 5-week cognitive training (N=12) or an equivalent education based control intervention (N=13). Participants completed a visual attention task for faces and scenes while undergoing an fMRI scan where task demands required them to attend to goal-relevant stimuli and ignore goal-irrelevant stimuli. Preprocessing of this data was carried out with AFNI and multivariate event-related analyses were conducted using Partial Least Squares (PLS). Post-attention training, we observed (i) increased recruitment of brain regions overlapping with the FPN during task trials requiring enhancement of goal relevant

information and (ii) increased recruitment of DMN regions during task-trials requiring suppression of goal-irrelevant information. In summary, our results support our previous findings of enhanced functional engagement of frontal and parietal brain regions associated with executive control post-training. Here we provide novel evidence for broader network changes following attention training. Specifically we observed a differential pattern of functional activation during enhancement (FPN) or suppression (DMN) of stimuli based on the current goal state. These findings suggest that attention regulation may impact modulation of large-scale brain networks based on goal relevance. Future work will investigate the relationship between this enhanced functional engagement post-training and measures of cognitive performance and real-world functioning in older adults.

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Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

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Topic: F.01. Human Cognition and Behavior

Support: Portuguese Foundation for Science and Technology (FCT; SFRH/BD/90078/2012)

European Commission (FP7): "SwitchBox" (Contract HEALTH-F2-2010-259772)

Title: Comparing in-Person and Telephone Approaches to Videoconference - based cognitive assessment - an exploratory study with older individuals

Authors: *T. C. CASTANHO, L. AMORIM, P. MOREIRA, J. MARIZ, A. SILVA, J. PALHA, N. SOUSA, N. SANTOS;
Life and Hlth. Sci. Res. Inst. (ICVS), Sch. of Hlth. Sci., Braga, Portugal

Abstract: The increase in average life expectancy is a worldwide phenomenon responsible for a raise in the elderly population. Screening for cognitive impairment in older adults is still a difficult practice, but significant for clinicians and researchers who work with geriatric patients. In neuropsychological evaluation, in-person testing is considered the most effective mode of assessment however it can be limiting in reaching those with functional or other limitations. Taking these into consideration, feasible and rapid assessment tools are needed to assist in

cognitive diagnosis in clinical and psychological practice. The Telephone Interview for Cognitive Status Assessment (TICS), with a delayed recall item (modified, M), is one of the most widely used instruments to this end. Here the purpose of the current study was to determine whether cognitive testing via video-conferencing (VC; Skype®) using the TICSM provided comparable results with its application by telephone and with the Mini-Mental State Examination (MMSE) administered face-to-face. Fifty community dwellers aged 57 to 95 (mean = 71.90, SD = 1.298), still residing full-time in the community or institutionalized in day care centers, were randomly selected from registries of local health centers and day care centers. All participants were tested on cognitive performance under three experimental conditions: VC, face-to-face and telephone. Significant associations were obtained between the three administration methods, with the VC administration method yielding comparable results to the traditional telephone application and face-to-face evaluations of the MMSE. The linear regression model analysis indicated that age, gender, education and provenience explained 43.4% of the variance of the TICSM total score via VC, and 35.5% of the variance of the TICSM total score administered by telephone. This study demonstrates that TICSM scores obtained via VC are similar to those obtained via telephone evaluation and the "gold standard" (MMSE) in the face-to-face manner. The results also support the range of settings where the TICSM can be applied and its good acceptability. An alternative to travel to remote centers for routine or specialized services, health services via technologies can provide those in rural areas and nursing homes with substantial support.

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Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

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Program#/Poster#: 622.03/X43

Topic: F.01. Human Cognition and Behavior

Title: Spatial reconstruction and spatial pattern separation in young and older adults

Authors: *R. CLARK[1,2], A. TAHAN[3], P. D. WATSON[4], N. COHEN[4], J. SEVERSON[5], M. VOSS[2,3];
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Iowa, Iowa City, IA; [4]Dept. of Psychology and Interdepartmental Neurosci. Program, Univ. of Illinois Urbana-Champaign, Urbana-Champaign, IL; [5]Digital Artefacts, Iowa City, IA

Abstract: The hippocampus experiences significant anatomical and functional change during aging. Tasks that can be administered repeatedly with stable performance are needed for reliably assessing hippocampal functioning as a reference for detecting decline in performance due to aging or disease or improvement from change in lifestyle behaviors. The goal of the current study was to determine age-related performance differences and reliability of repeated testing of two tasks that have been proposed to measure hippocampal functioning. Fifty-four young (18-30 yrs; 28 F) and 30 older participants (60-80 yrs; 21 F) completed 4 experimental visits. All individuals completed a tablet-based spatial reconstruction (SR) task and a computer-based spatial pattern separation (SPS) task. The SR task involves delayed spatial reconstruction of unique layouts of novel objects. Error measurements include misplacement metrics and a relation-dependent swap metric, primarily targeting item-pair relation memory. The SPS task involves presentation of a target stimulus followed by two cues, one of which matches the location of the target. Smaller distances between cues leads to greater memory representation interference between, thus targeting the resolution of memory representations. Half of the participants performed the SR once and the SPS three times, while the other half performed the SPS once and the SR three times. As expected, young adults performed better than older adults on the SR task on all error metrics (swap metric: $F(1,81)=11.062$, $p<.001$). However, there was no main effect of age on the SPS task ($F(1,328)=2.319$, ns). No session effect was found for either the SR task (swap metric: $F(2,76)=.582$, ns) or the SPS task ($F(2,82)=1.635$, ns), nor was an age by session interaction found for either task. Interestingly, the SR task swaps error metric was negatively correlated with SPS task accuracy at lower levels of spatial interference across all individuals (Young: $r=-.279$, $p=.043$; Older: $r=-.445$, $p=.016$), and at higher levels of spatial interference only for older adults ($r=-.571$, $p=.019$). However, swap error rate on the SR task was not correlated with processing speed as measured by Trails A (Younger: $r=-.152$, ns; Older: $r=.150$, ns), supporting the idea that the association between SPS and SR performance is due to a commonality in spatial memory processing. These results indicate that both tasks can be administered repeatedly for both young and older adults with good test-retest reliability. The results also indicate that while the SR and SPS task may both tap memory constructs, item-pair swap rate in the SR task is more sensitive to age-related differences in hippocampal function.

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Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

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Topic: F.01. Human Cognition and Behavior

Support: SwedishResearchCouncil(2008-2356)

Title: Functional correlates of personality & facial perception in old and young adults

Authors: *N. PERSSON[1,2], N. C. EBNER[3], T. LIN[3], H. FISCHER[2,4];
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Abstract: Daily social interaction involves perception of emotional faces. Individual personality is of vital importance for how we perceive and interact with the outer world. Personality has been associated with age sensitive structures in the frontal cortices, and emotional perception. The literature investigating the link between personality, facial perception and BOLD activation is scarce. We assessed the influence of personality on peak fMRI BOLD activation in fronto-parietal areas in response to happy, neutral, and angry faces in a sample of younger (n= 30, 20-31 years) and older (n=31, 65-74 years) men and women. A series of Structural Equation Models was specified to evaluate the influence of age and personality on BOLD activation to emotional faces, contrasted with neutral faces. The behavioral measures included aspects of neuroticism (N), extraversion (E), and openness (O), assessed by a standard questionnaire (NEO-PI) during a first session. During the second session (fMRI), participants worked on the Facial Expression Identification Task that presented them with photos of old and young neutral, happy, and angry faces, randomly intermixed. Images were acquired using a 3T scanner (Siemens Magnetom Tim Trio). Onehundred and sixty functional images each were acquired with a T2*-weighted echo-planar sequence. Thirty-nine oblique axial slices were positioned parallel to the AC-PC line and acquired interleaved. A 1 × 1 × 1 mm T1-weighted image was used for co-registration with functional images. Processing of emotional faces was associated with increased activation in the medial frontal gyrus (MFG) and the post central gyrus (PCG), (FWE corrected). Older adults showed lesser degree of N and O than their younger counterparts. There were no reliable group differences in E. Older age predicted greater activity in PCG to angry faces compared to neutral faces, but there was no significant association for MFG. Extraverted subjects showed greater activity to angry than neutral faces after age was accounted for. E also predicted greater activity in MFG in response to happy than neutral faces, but the association was gone after age was taken into account. A trend was present for lesser activity in the PCG to angry than neutral faces for more neurotic subjects, but the association did not hold when adjusting for age. O was not related to activation to emotional faces in any of the ROIs.Our findings suggest that higher degree of extraversion is particularly important for BOLD activation in age-sensitive key structures in emotional processing. Greater activation of fronto-parietal networks to emotional faces in extroverted subjects may reflect increased use of cognitive control.

Disclosures: **N. Persson:** None. **N.C. Ebner:** None. **T. Lin:** None. **H. Fischer:** None.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 622.05/X45

Topic: F.01. Human Cognition and Behavior

Support: NIH R21 Grant AG044862

Title: Fatigue and fatigability in young and older adults

Authors: ***S. BURKE**[1], I. SAMUEL[2], B. KLUGER[3], M. DING[2];
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Abstract: Fatigue is associated with increased mortality in older adults and is the leading cause of activity restrictions in this population. Unfortunately, our understanding of the causes of fatigue in older adults is quite limited and there are no proven treatments. Typically, fatigue is assessed by questionnaires. Cognitive fatigability, in contrast, is defined as changes in behavioral performance that occur during a sustained cognitive activity and is a more objective measure. The goal of this study is to compare cognitive fatigability in young and older adults. Naively, one expects that older adults are more fatigable than young. However, considering that during cognitive performance, older adults tend to adopt the resource-preserving strategy of taking longer to respond, we hypothesized that the opposite is true. To test the hypothesis we recruited a group of 18 healthy older subjects between the ages of 60 and 87 and a group of healthy young adults between the ages of 18 and 33. They were asked to perform a 3 hour continuous cued Stroop task. Two results were found. First, at the baseline (first 30 minutes of the task), the young group had faster reaction times but committed more errors than the aged group. Second, the aged group did not show markedly decreased performance (i.e., slowed reaction time and increased error rate) as time-on-task increased, whereas the young group exhibited significantly slowed reaction times and higher error rate as time-on-task increased, giving rise to higher cognitive fatigability. These results, consistent with our hypothesis, suggest that a conservative behavioral strategy that trades speed for accuracy helps to minimize resource depletion in the face of prolonged cognitive performance. Key words: Cognitive fatigability, fatigue, aging.

Disclosures: **S. Burke:** None. **I. Samuel:** None. **B. Kluger:** None. **M. Ding:** None.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

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Program#/Poster#: 622.06/X46

Topic: F.01. Human Cognition and Behavior

Support: EU FP7- IEF 330792 (DynViB)

BMBF BCCN Göttingen (01GQ1005B)

EU Human Brain Project (grant no. 60402).

Title: Dynamics of resting state functional connectivity through the human adult lifespan

Authors: *D. BATTAGLIA[1,2], E. C. A. HANSEN[1,3], P. RITTER[4,5,6], V. JIRSA[1];
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Abstract: The aging brain undergoes anatomical alterations, but also transformations of the flexible way in which brain regions interact during cognition. In particular, functional connectivity in the resting state, describing spontaneously emergent correlations between the activity of different areas, distinctly displays age-related changes. Here, we show that aging also profoundly impacts on the dynamics of this functional connectivity. We reveal a characteristic switching, markedly slowing down with age, between epochs of meta-stable functional connectivity and transients of fast functional network reconfiguration. Furthermore, we identify communities of functional links, rather than network nodes, whose temporal fluctuations become increasingly anti-correlated in elderly subjects. Such manifest remodeling of functional connectivity dynamics discloses aspects of cognitive aging that cannot be captured by variations of structural and time-averaged functional connectivity. Its statistical parameterization allows then predicting a subject's age with superior accuracy, opening the way to the design of performing biomarkers with perspective clinical relevance. In particular, exploiting positive synergies between information about Functional Connectivity Dynamics, structural connectivity and time-averaged FC, we are able to predict the age of a single subject with an unprecedented precision of ±5 years, over an age span between 18 and 80 years. We finally show preliminary evidence that our Functional Connectivity Dynamics analyses predict also performance in simple

tasks, correlating thus to subject-specific cognitive flexibility beyond general trends due to anagraphic age.

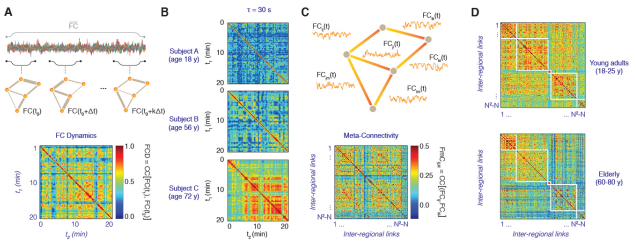

Figure caption: A. Functional Connectivity Dynamics (FCD) analysis, i.e. correlation between functional networks observed at different times. B: FCD slows down and "crystallize" with aging. C: Meta-Connectivity (MetaFC) analysis, i.e. correlation between time variation of functional links strenghts. D: anticorrelated meta-links develop with aging.

Disclosures: D. Battaglia: None. **E.C.A. Hansen:** None. **P. Ritter:** None. **V. Jirsa:** None.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

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Program#/Poster#: 622.07/X45

Topic: F.01. Human Cognition and Behavior

Support: NIH grant AG047334

NIH grant AG034613

Title: Contributions of hippocampal and striatal tract integrity to mnemonic discrimination across the lifespan

Authors: *I. J. BENNETT[1,2], C. E. L. STARK[2,1];
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Abstract: The striatum (caudate, putamen) is traditionally implicated in implicit forms of learning and memory (Squire, 1992). However, converging evidence indicates that the striatum also contributes to explicit, episodic memory. For example, individuals with striatal dysfunction exhibit episodic memory deficits (e.g., Parkinson's disease; Elgh et al, 2009) and striatal lesions

can produce memory impairments that mimic hippocampal damage (Yin & Knowlton, 2004). Moreover, functional neuroimaging studies have shown both hippocampal and striatal engagement during item recognition (Scimeca & Badre, 2012) and paired-associate learning (Mattfeld & Stark, 2010). Successful performance on these tasks requires discrimination of novel events from previously encountered events. This type of mnemonic discrimination is thought to rely on pattern separation, a computational process by which unique representations are generated for each event (Yassa & Stark, 2011). Using diffusion tensor imaging (DTI), our lab has previously shown that mnemonic discrimination is related to integrity of hippocampal tracts, including the fornix (Bennett et al, 2014), in healthy adults across the lifespan. In the current study, we tested the hypothesis that striatal tract integrity also relates to mnemonic discrimination. Participants (n = 112, 20-89 years) underwent whole-brain DTI to obtain measures of hippocampal (fornix) and striatal (caudate-frontal) tract integrity (fractional anisotropy, mean diffusivity). They also performed a modified item recognition task, the Mnemonic Similarity Task (Kirwan & Stark, 2007), which provides measures of mnemonic discrimination (correct "similar" responses to lure objects that are similar to memory set objects) and traditional recognition memory (correct "old" responses to repeated memory set objects). Results revealed age-related declines in fornix and caudate-frontal tract integrity, and in mnemonic discrimination, but not recognition memory. Separate regression analyses further revealed that increased fornix and caudate-frontal tract integrity was related to better mnemonic discrimination. After controlling for the effect of age on white matter integrity, however, only the relationship between fornix integrity and mnemonic discrimination remained significant. These preliminary findings indicate that mnemonic discrimination is mediated by integrity of tracts within the hippocampal, but not striatal, memory system. Additional research will be necessary to determine if integrity of other striatal tracts relate to mnemonic discrimination, or if the striatal network mediates other components of episodic memory.

Disclosures: I.J. Bennett: None. **C.E.L. Stark:** None.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 622.08/X48

Topic: F.01. Human Cognition and Behavior

Title: Discovery and characterization of potent biphasic a5GABAA receptor modulators

Authors: *M. SOH[1], R. MCGEARY[2], J. LYNCH[1];
[1]Queensland Brain Inst., Brisbane, Australia; [2]Sch. of Pharmacy, The Univ. of Queensland, Brisbane, Queensland, Australia

Abstract: Therapeutic drugs targeting $GABA_AR$s are used as anxiolytics, sedatives, and antiepileptics. These drugs are allosteric positive modulators of $GABA_AR$s that enhance GABA activity. As these drugs non-selectively target many $GABA_AR$ subtypes causing unwanted side effects, subunit-specific drugs are now desirable. Positive modulators selective for α_5GABA_ARs have shown promising results in treating cognitive symptoms of schizophrenia and age-related dementia, whereas α_5GABA_AR negative modulators have proven worth as cognition enhancers, in post-stroke recovery and prevention of general anesthetic-induced amnesia, without causing sedation and anxiety. The aim of this project is to discover and characterize novel α_5GABA_AR selective compounds. This was accomplished by screening a library of synthetic compounds on HEK cell-transfected $\alpha_5\beta_3\gamma_{2L}$ $GABA_AR$s using high-throughput YFP-based anion influx assay. Modulation on other $GABA_AR$ subtypes ($\alpha_1\beta_2\gamma_{2L}$, $\alpha_5\beta_2\gamma_{2L}$) and drug binding sites were also explored using functional studies on two-electrode voltage clamp electrophysiology (TEVC). To prepare for TEVC, *Xenopus borealis* frogs were anesthetized with MS-222 and surgically incised to obtain the oocytes, which were digested and injected with $GABA_AR$ mRNAs. TEVC recordings revealed that isomeric compounds RM 68, RM 69 and RM 70 are potent $GABA_AR$ modulators. These isomers, except RM 69, demonstrated biphasic modulation, selectively potentiating α_5GABA_ARs in the nM (sometimes pM) range, but inhibiting $GABA_AR$s non-selectively at higher μM concentrations. Removing mercaptoacetaldehyde from RM 68 to give RM 96 eliminated its α_5GABA_AR selectivity. Flumazenil managed to neutralize the potentiation of GABA responses by the 4 compounds, suggesting that the potentiating effect of these compounds was modulated via the benzodiazepine site. RM compounds can be potential leads to design novel subtype specific drugs for $\alpha_5$related disorders and to study the pharmacology of α_5GABA_ARs.

Disclosures: **M. Soh:** A. Employment/Salary (full or part-time):; Queensland Brain Institute. **R. McGeary:** None. **J. Lynch:** None.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 622.09/Y1

Topic: F.01. Human Cognition and Behavior

Support: NIH R37 AG-11230

Title: Age differences in regional myelin content and white matter organization in healthy adults: Comparing myelin water fraction and diffusion tensor imaging

Authors: *M. ARSHAD[1], J. A. STANLEY[2], N. RAZ[3];
[1]Wayne State Univ., Detroit, MI; [2]Psychiatry and Behavioral Neurosci., Wayne State Univ. Sch. of Med., Detroit, MI; [3]Psychology, Inst. of Gerontology, Wayne State Univ., Detroit, MI

Abstract: Much of the extant literature relies on indices derived from diffusion tensor imaging (DTI), e.g., fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD), to characterize age related differences in cerebral white matter. Despite growing evidence, differences in FA or RD are frequently interpreted as differences in myelination. In this study we compare FA to a more specific index of myelin content, Myelin Water Fraction (MWF), across multiple regions of interest representing association, projection and commissural pathways in a sample of 40 healthy adults (mean age = 52.0, SD = 18.9 years). Regions of interests were mapped from standard space to subject space, where all DTI and MWF measurements were made. The relationship between MWF and age was quadratic and the largest age differences were noted in the superior longitudinal fasciculus (SLF) and internal capsule anterior limb (ALIC), followed by inferior fronto-occipital fasciculus (IFOF), genu and splenium of corpus callosum, alhough the effect sizes do not differ significantly. No age differences were observed in the posterior limb of IC (PLIC). In contrast, the FA analysis revealed linear age differences, largest in IFOF and Genu, moderate in the Splenium and ALIC, lesser in the SLF and none in the PLIC. RD showed linear and quadratic age differences in ALIC and splenium. AD evidenced uniform linear and quadratic age differences across all regions. Correlations between MWF and DTI indices, after Bonferroni corrections, were not significant, except for SLF AD-MWF pairing. Thus, we find different relationships of MWF and DTI indices with age, across the white matter regions sampled here. The quadratic relationship between MWF and age is consistent with the continuing myelination of sub-cortical white matter tracts into adulthood. These results support the growing awareness that DTI indices are not a reflection of a myelination and caution should be taken when interpreting age differences in DTI indices.

Disclosures: **M. Arshad:** None. **J.A. Stanley:** None. **N. Raz:** None.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

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Program#/Poster#: 622.10/Y2

Topic: F.01. Human Cognition and Behavior

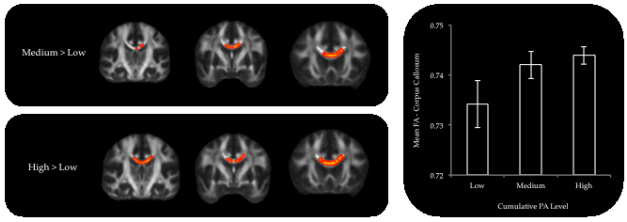
Support: MRC Life-Long Health and Well-Being grant (G1001354)

National Institute for Health Research Oxford Biomedical Research Centre Programme

Title: Physical activity levels and white matter microstructure in community-dwelling older adults

Authors: *C. SEXTON[1], N. FILIPPINI[1], E. ZSOLDOS[1], A. MAHMOOD[1], S. SABIA[2], A. SINGH-MANOUX[2], M. KIVIMAKI[2], H. JOHANSEN-BERG[1], K. EBMEIER[1];
[1]Univ. of Oxford, Oxford, United Kingdom; [2]Univ. Col. London, London, United Kingdom

Abstract: Cross-sectional studies have previously shown that cardiorespiratory fitness is positively correlated with white matter volume and integrity within the corpus callosum (1,2). Here, we use Diffusion Tensor Imaging to examine the relationship between physical activity (PA) levels and the corpus callosum in 306 members of the Whitehall II cohort (72 females, age 68.9 ± 4.9 years). PA was measured using a modified version of the Minnesota leisure-time PA questionnaire at 4 time-points (1997-99, 2002-04, 2007-09, 2012-13), and DTI acquired at a single time-point (2012-14) (3). For prospective and cross-sectional analyses, PA was classified at each time-point as low, medium or high and assigned a score of 0, 1 or 2, respectively. Low PA corresponded to < 1 hour moderate and < 1 hour vigorous PA per week, and high PA to ≥ 2.5 hours moderate or ≥ 1 hour vigorous PA per week. For cumulative analyses, PA score was summed across all time-points, and classified as low (total score 0-2), medium (3-5) or high (6-8). Analysis of DTI data was carried out using Tract-Based Spatial Statistics, with voxel-wise statistics performed using Randomise. F-tests were used to examine the overall effects of PA on fractional anisotropy (FA) values within the corpus callosum, and post-hoc t-tests used to assess group differences. Age and gender were included as covariates in all analyses, and the significance threshold set at $p<0.05$ using threshold-free cluster enhancement. At each individual time-point, PA was not found to be significantly associated with FA. In cumulative analyses, though, FA values were significantly different between PA groups. Post-hoc t-tests demonstrated that FA was significantly greater in both the medium and high PA groups compared with the low PA group (Figure). In conclusion, our results support the hypothesis that cumulative levels of PA are associated with white matter integrity in older adults. References 1. Johnson et al. Neuroimage. 2012;59(2):1514-23. 2. Erickson et al. Neurobiol Aging. 2007;28(2):179-85. 3. Filippini et al. BMC Psychiatry. 2014;14:159.



Disclosures: **C. Sexton:** None. **N. Filippini:** None. **E. Zsoldos:** None. **A. Mahmood:** None. **S. Sabia:** None. **A. Singh-Manoux:** None. **M. Kivimaki:** None. **H. Johansen-Berg:** None. **K. Ebmeier:** None.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 622.11/Y3

Topic: F.01. Human Cognition and Behavior

Support: MRC

Title: Age-related changes in cerebral correlates of voice processing

Authors: ***J. ZHANG**[1,2], F. W. SMITH[3], B. L. GIORDANO[2], M.-H. GROSBRAS[2], G. A. ROUSSELET[2], P. BELIN[2];
[1]Ctr. for Vital Longevity, Univ. of Texas at Dallas, Dallas, TX; [2]Inst. of Neurosci. and Psychology, Univ. of Glasgow, Glasgow, United Kingdom; [3]Sch. of Psychology, Univ. of East Anglia, Norwich, United Kingdom

Abstract: Pervasive age-related brain atrophy, including in auditory cortex, creates the necessity of studying whether and how voice processing changes with age. To address this issue, in an fMRI study we manipulated vocal and non-vocal signals and measured the relationship between age and brain functions for voice processing by applying both univariate and multivariate analysis. Sixty healthy adults (20-86 years, M = 51.2 years, SD = 18.2) passively listened to sounds with eyes closed while being scanned. The paradigm consisted of a classical voice localizer scan (Belin et al., 2000) contrasting blocks of vocal vs non-vocal sounds to identify the temporal voice areas (TVA), which mostly cover the middle and anterior parts of the bilateral superior temporal sulcus (STS) (Belin et al., 2000). The stimuli had 40 8-sec blocks of sounds. Half of the blocks had only vocal sounds, and the other half had only non-vocal sound. Both univariate (General Linear Model, GLM) and multivariate approaches were used. For the

multivariate analysis, we used leave-one-trial-out cross validation to train and test a linear support vector machine (SVM). Results showed that TVAs were responsive to voice processing across the whole age range in both univariate and multivariate analysis. To study how voice processing changes with age, we conducted correlations of activity/classification accuracy with age for the univariate and multivariate approach respectively. Univariate analysis did not show significant negative correlation of activity with age for the vocal vs non-vocal contrast. In contrast, multivariate analysis showed that the vocal minus non-vocal accuracy in bilateral TVAs declined with increasing age. Both the univariate and multivariate analysis had a significant positive correlation in activity/accuracy with age, with univariate analysis showing that activity in bilateral postecentral regions increased with age whereas multivariate analysis showing that the classification accuracy difference between vocal and non-vocal in medial frontal and right precentral regions increased with age. The results suggest that multivariate and univariate analysis had different sensitivity to age-related changes in voice processing. Multivariate pattern analysis had an age-related decline in voice processing, with less sensitivity to differentiating vocal from nonvocal sounds in bilateral temporal regions in response to aging. Univariate analysis seems to be less sensitive to detecting age-related impairment in voice processing. Both multivariate and univariate seem to be sensitive to the age-related increasing recruitment of regions in the non-auditory cortex.

Disclosures: J. Zhang: None. **F.W. Smith:** None. **B.L. Giordano:** None. **M. Grosbras:** None. **G.A. Rousselet:** None. **P. Belin:** None.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 622.12/Y4

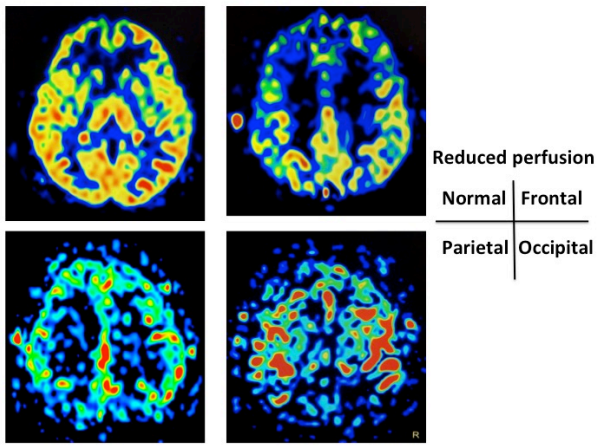
Topic: F.01. Human Cognition and Behavior

Title: Arterial spin labelling (ASL) may be useful for diagnosing various types of Parkinson's disease with dementia

Authors: *K. ABE[1], T. HAYASHI[2], M. YAMAMOTO[2], N. AKIYAMA[2], M. FUJITA[2]; [1]Dept. of Community Hlth. Med. and Neurol., Hyogo Col. of Med. Grad. Sch. of Medic, Nishinomiya-Shi, Japan; [2]Neurol., Fujita Shinkeinaika Clin., Higashiosaka, Japan

Abstract: Purpose: To determine whether arterial spin labeling (ASL) can be used to evaluate regional cerebral blood flow (CBF) patterns in various types of Parkinson's disease (PD) with

dementia. Subjects and Methods: Thirty five PD patients (15 Male/19 Female, Age 73.1±6.5 (mean±SD) years, disease duration7.55±3.3) who met a Japanese PD diagnosis criteria and 35 age and sex normal controls were scanned by using a pseudo-continuous arterial spin labeling (PCASL) method with a 1.5 Tesla MRI unit (Achieva A-series; Philips Medical Systems, Best, The Netherlands). Clinical signs were evaluated by unified Parkinson's disease rating scale (UPDRS), minimental state exmination (MMSE), frontal assessment batery (FAB), Montral cognitive assessment (MOCA). Regional cerebral blood volume (CBF) was compared in the frontal, the parietoposterial, and the posterior cortex using region-of-interest analysis. Results: PD patients had UPDRS with 33.9±5.2 MMSE with 24.0±3.9, FAB with 13.5±3.7, MOCA with 21.7±5.7. PD patients showed four regional CBF patterns. The first group had normal regional CBF patterns comparing with those of normal controls. The second group had reduced frontal cortex regional CBF patterns comparing with those of normal controls. The third group had reduced parietoposterial cortex regional CBF patterns comparing with those of normal controls. The fourth group had reduced posterial cortex regional CBF patterns comparing with those of normal controls. Conclusion: This is a study to detect four patterns of hypoperfusion in the cortex in PD patients using ASL perfusion MRI. Because ASL perfusion MRI is completely noninvasive and can, therefore, safely be used for repeated assessments, this method can be used to monitor treatment effects or disease progression in PD.



Disclosures: **K. Abe:** None. **T. Hayashi:** None. **M. Yamamoto:** None. **N. Akiyama:** None. **M. Fujita:** None.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 622.13/Y5

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant NS082386

NIH Grant AG044862

NINDS K23NS060660

Title: Anatomical substrate of fatigue in Parkinson's disease

Authors: *Q. ZHAO[1], H. HUANG[1], J. TANNER[2], C. PRICE[2], B. KLUGER[3], M. DING[1]; [1]J. Crayton Pruitt Family Dept. of Biomed. Engin., [2]Dept. of Clin. and Hlth. Psychology, Univ. of Florida, Gainesville, FL; [3]Univ. of Colorado, Denver, CO

Abstract: Nonmotor symptoms in Parkinson's disease (PD) are increasingly recognized as a significant source of suffering and disability. In particular, fatigue affects approximately half of all PD patients and is reported by one third to be their single most disabling symptom. The pathogenesis of fatigue in PD remains unknown, however, and we have no effective treatments. Here, we performed a voxel-based morphometry (VBM) analysis to examine the neuroanatomical basis of fatigue in PD. Forty nine patients clinically diagnosed with idiopathic tremor dominant PD without dementia (42 male, 7 female) and forty two age- and sex- matched controls (37 male, 5 female) enrolled. Imaging included T1-weighted structural scans acquired with trait-level fatigue assessed by Fatigue Severity Scale (FSS) within 24 hours of the MRI. Dividing PD patients into two groups: with fatigue (FSS>4, 25 subjects) and without fatigue (FSS<4, 24 subjects), we found that PD patients with fatigue had reduced gray-matter volume in caudate and putamen relative to PD patients without fatigue ($P<0.05$ FDR corrected). The involvement of insula in fatigue was further revealed by a ROI-based multiple regression analysis. In contrast, no fatigue-related structural atrophy was found in controls. These results provide evidence for a central origin of fatigue involving the frontal-striatal network and insula within PD.

Disclosures: Q. Zhao: None. **H. Huang:** None. **J. Tanner:** None. **C. Price:** None. **B. Kluger:** None. **M. Ding:** None.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 622.14/Y6

Topic: F.01. Human Cognition and Behavior

Support: NIA K23 AG036852, NIMH MH/NIMH/R25/MH071544

Title: Validation of olfactory identification deficit as a biomarker of Alzheimer's disease

Authors: *E. LAZAR[1], M. WOODWARD[1], C. AMRUTKAR[1], J. HAGEMEIER[1], H. SHAH[1], R. BENEDICT[1], S. RAJAKRISHNAN[1], R. DOODY[2], L. YAN[1], K. SZIGETI[1];
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Abstract: Importance: With increased longevity the prevalence of AD in the elderly represents a major public health problem. Olfactory identification deficit (OID) may represent a parallel neurodegenerative process preceding the AD disease trajectory thus may have utility 1) as a screening tool in the primary care setting, 2) in identifying presymptomatic individuals for disease modifying therapy,3) in enriching aMCI trials with conversion as the primary outcome measure. Objective: To evaluate smell identification as a biomarker for AD by assessing its utility in differentiating normal aging from an amnestic disorder and determining its predictive value for conversion from aMCI to AD. To correlate the clinical olfactory deficit with neuroanatomical changes assessed by structural MRI. Design: There are three components: 1) it is powered as a cross-sectional case-control study to evaluate the sensitivity and specificity of OID in differentiation normal aging from an amnestic disorder; 2) an exploratory longitudinal study of aMCI subjects with at least one year follow up to evaluate the utility of OID in predicting conversion from aMCI to probabale AD by NINCDS-ARDA criteria; 3) a subset of subjects (27 NC, 15 aMCI and 37 AD) had structural MRI analysis. Participants: 566 participants 65 years or older were consented to participate (AD=262, aMCI=110, Controls=194). Results: Correlation trend test between odor identification and disease status was significant after correcting for age, sex, and ApoE in the model (p=1.52x10-59). ROC/AUC was similar for the 40 item UPSIT, the top 10 smells in our study, and the 10 item subset previously proposed. Smeller/non-smeller based on the 10 item subset with a cutoff of 7 (< = 7, non-smeller; > 7, smeller) had a sensitivity and specificity of 88% and 71% for identifying AD, and 74% sensitivity and 71% specificity for identifying an amnestic disorder. 36.4% of subjects with impaired olfaction and 17.3% with intact olfaction converted to AD (p=0.03).Volumetric analysis revealed differences in right hippocampal volumes between smellers and non-smellers in the aMCI stage. Olfactory memory is coded in the right hippocampus suggesting disease relevance and a central mechanism. OID measures a pure memory deficit and does it earlier. Conclusion: OID has sensitivity and specificity that are comparable or slightly inferior to other established biomarkers, with benefits such as ease of administration and low cost. Longitudinal studies exploring the time relationship between the trajectory of decline in olfactory identification and the development of an amnestic disorder are needed to further characterize the relationship.

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Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

Location: Hall A

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Program#/Poster#: 622.15/Y7

Topic: F.01. Human Cognition and Behavior

Support: 5P50AG025688-10

Title: Identification of initial visit factors predictive of cognitive maintenance or cognitive decline in memory clinic patients

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Abstract: Objective: Alzheimer's disease (AD) is a devastating neurodegenerative condition that currently has no cure. Due to significant personal and financial costs associated with treatment, it is of critical importance to identify the disease in its most incipient stages. Here, we use clinical assessment records to study characteristics of patients who either decline mentally or stay relatively stable over several years. We hope our findings will offer more insight into the probable trajectories of various patient groups, which could shed light towards more targeted treatment decisions from the very first visit. Methods: More than 10,000 record visits were initially extracted from the Emory University memory clinic database. Records were next grouped by patient and those with an initial Mini Mental State Examination (MMSE) of at least 24 and at least two years between first and last visits were divided into "Stable" and "Declining" groups representing patients whose MMSE scores changed less than 2 points and those whose scores decreased by more than 5 points respectively. The demographic and first cognitive testing variables of these Stable and Declining patient groups were characterized. Significant differences between these groups were tested using t-test or chi-squared statistics. In addition, to identify factors that influence changes between Stable and Declining groups, we performed logistic regression and Akaike information criterion (AIC) - based stepwise variable selection. Results: Descriptions of demographic and initial cognitive testing variables and significance of

differences between Stable and Declining groups are given in Table 1. Chi-squared proportions test revealed no differences in biological sex, handedness, or race between the two groups. Finally, logistic regression results indicate five baseline cognitive test scores that significantly predict decreasing mental state. Conclusion: Early diagnosis is a critical first step towards the goal of delaying the progression of dementia-related diseases. Our results shine light on initial visit demographic and cognitive scoring factors associated with stable or decreasing condition that may be capitalized upon to reduce the overall burden of the disease.

Table 1: Stable vs Declining patient characteristics

Demographic/Cognitive Initial Factor	Stable Patients (N=113)	Declining Patients (N=103)	P value
Handedness (%RH, %LH, %AMB)	90.27, 7.965, 0.885	90.29, 8.738, 0	N/A
Sex (% Male)	46.02	50.48	N/A
Race (%African American, %Caucasian)	19.47, 80.53	10.68, 89.32	N/A
Average Age at Exam [mean(SD)]	64.75 (9.408)	66.94 (9.046)	4.17E-02
Education yrs [mean(SD)]	16.83 (2.401)	14.96 (2.719)	1.03E-07*
MMSE Score [mean(SD)]	29.02 (1.275)	26.68 (1.8)	3.51E-23
Clock Score [mean(SD)]	12.1 (1.635)	11 (2.76)	2.29E-04*
Fwd Digit Span total [mean(SD)]	9.028 (2.146)	8.8 (2.34)	2.32E-01
Rev Digit Span total [mean(SD)]	6.704 (2.015)	5.56 (1.898)	1.94E-05*
Trails A Time (sec) [mean(SD)]	38.57 (38.11)	60.71 (42.79)	5.67E-05*
Time A Errors [mean(SD)]	0.1495 (0.4076)	0.2292 (0.5521)	1.20E-01
Trails B Time (sec) [mean(SD)]	95.75 (87.58)	219.9 (206.7)	2.38E-08*
Trails B Errors [mean(SD)]	0.570 (0.923)	2.352 (5.28)	3.67E-04*
Geriatric Depression Scale [mean(SD)]	1.404 (1.597)	2.577 (2.565)	7.93E-05*
Time between first and last visit (yrs) [mean(SD)]	4.585 (2.141)	5.294 (1.797)	4.71E-3
Summary statistics for Stable and Declining patients for a variety of demographic (first five			

rows) and cognitive measures. One way two sample t test p values are given in the right most column. Significance satisfies Bonferonni corrected p value

Disclosures: **W.D. Dunn:** None. **R. Chen:** None. **L. Zhang:** None. **E.E. Hecht:** None. **A.I. Levey:** None. **D.A. Gutman:** F. Consulting Fees (e.g., advisory boards); Memorial Sloan Kettering Dermatology Division-- Consultant.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 622.16/Y8

Topic: F.01. Human Cognition and Behavior

Support: ZonMw95110091

Title: PDE4 inhibition in young healthy adults improves memory: a translational approach

Authors: ***M. VAN DUINEN**[1], A. SAMBETH[2], A. BLOKLAND[2], J. PRICKAERTS[1]; [1]Psychiatry and Neuropsychology, [2]Neuropharm. and Neuropsychology, Maastricht Univ., Maastricht, Netherlands

Abstract: Selective phosphodiesterase (PDE) inhibition has been considered as an interesting target for cognition enhancement. There are 11 different PDEs and only some PDEs have been related to memory enhancement: PDE1-5 and PDE9. The classic PDE type 4 inhibitor rolipram has repeatedly shown to enhance memory performance in rodents, yet its clinical application is limited due to severe emetic side effects. More recently, PDE4-Is have been found with a far more favorable side effect profile. After we showed memory improvement in rodents after treatment with the selective PDE4 inhibitor roflumilast, we initiated a trial with roflumilast to evaluate its cognition enhancing potential in young healthy adults. Memory and attention performance were assessed and EEG was recorded simultaneously. Acute oral roflumilast administration (100 mcg, 300 mcg and 1000 mcg) was applied in a double-blind cross-over placebo controlled design. Healthy adults (n=20) receiving a single oral dose of 100 mcg of roflumilast showed a statistically significant improvement with respect to the number of correct words recalled in the verbal learning task (VLT) after the third learning trial as compared to placebo. Roflumilast did not improve delayed recall scores in the VLT. Evaluation of the EEG

measurements (event-related potentials) during the VLT testing revealed a higher P600 amplitude after receiving a single oral dose of 100 mcg of roflumilast as compared to placebo. The P600 has repeatedly been related to memory processes and supported the effects on the improved memory performance. No effects of roflumilast on attention were discovered as assessed with the Stroop. Side effects were reported in some subjects with the higher doses (e.g. nausea), in particular after 1000mcg roflumilast. No side effects were found with the effective dose. We are the first to show that PDE4-I can improve memory performance in unaffected healthy young adults. This finding implies that roflumilast, by preventing the breakdown of cAMP by specific phosphodiesterases, optimizes memory. This data offers a promising pharmacological perspective for the treatment of memory impairment. Moreover, PDE-4 remains present in the older brain, which renders PDE4-Is an attractive target for memory impairment related to aging.

Disclosures: M. Van Duinen: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; ZonMw95110091, Takeda Development Centre Europe Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Takeda Development Center Americas, Inc.. F. Consulting Fees (e.g., advisory boards); Takeda Development Center Americas, Inc. **A. Sambeth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Takeda Development Center Americas, Inc. **A. Blokland:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Takeda Development Center Americas, Inc. **J. Prickaerts:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Takeda Development Center Americas, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Takeda Development Center Americas, Inc.. F. Consulting Fees (e.g., advisory boards); Takeda Development Center Americas, Inc..

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

Location: Hall A

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Program#/Poster#: 622.17/Y9

Topic: F.01. Human Cognition and Behavior

Support: FAPERGS

CNPq

IBRAVIN

Title: The effect of chronic consumption of purple grape juice on memory, bdnf and histone h4 acetylation levels in elderly residents in southern Brazil

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Abstract: Purple grape juice consumption by presenting phenolic compounds, has been described as an important strategy able to improve cognitive functions, especially during the aging process. However, the molecular bases associated with these beneficial effects are not yet elucidated. The present study aimed to investigate the effect of chronic consumption of purple grape juice on memory, plasma levels of brain-derived neurotrophic factor (BDNF) and histone H4 acetylation levels in leukocytes of healthy elderly residents in Porto Alegre city, Rio Grande do Sul, Brazil. This study was approved by the Ethics Committee on Human Research of the Methodist University with IPA on 04/12/2014, number 900.767. Forty one volunteers of both genders (4 male and 37 female) were recruited to take part in this experiment. They were instructed to consume 400ml daily of red purple juice, provided by the researchers, for 30 days in time not specified. For BDNF and histone H4 acetylation levels analyses, the volunteers underwent to two blood collections: before the intervention and after 30 days of juice consumption. These assays were performed using commercial kits (ELISA), according to the manufacturer's instructions. The Mini Mental State Examination test (MMSE) was also applied before and after the intervention in order to assess the memory. The Wilcoxon test revealed that there was no statistically significant change in BDNF and acetylation of histone H4 levels ($p > 0.005$) in the pre and post intervention periods. However, the paired t-test showed statistically significant difference, with higher scores in the post intervention period ($p = <0.001$). Conclusion: Chronic consumption of purple grape juice shown to improve memory of elderly people, which is not seem to be associated with the modulation of peripheral BDNF and histone

H4 acetylation levels. Additional work will be required to investigate the molecular mechanism behind this phenomenon.

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Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

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Topic: F.01. Human Cognition and Behavior

Support: R01 AG030311-06A1

Title: Age-related differences in the salience network: behavioral implications for executive function and affect

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Abstract: The salience intrinsic connectivity network is comprised by two dissociated subsystems, implicated in a variety of psychological phenomena that are critical for healthy aging. The dorsal salience subsystem includes regions important for executive function such as dorsal anterior insula and mid cingulate cortex; the ventral salience network includes regions implicated in affective experience such as ventral anterior insula, anterior cingulate cortex and amygdala (Seeley et al., 2007; Touroutoglou et al., 2012). In this study, we examined the age-related differences in the two salience subsystems and the behavioral implications of these differences. We found that the intrinsic connectivity within the dorsal salience subsystem decreases with age. In contrast, the connectivity within the ventral salience subsystem is preserved with age, and even increased between some of its nodes such as the ventral anterior insula and amygdala. Furthemore, using mediation analysis, we found that age-related declines in executive function are mediated by decreased connectivity within the dorsal salience subsystem, whereas age-related changes in negative affect are mediated by altered connectivity within the ventral salience subsystem. Taken together, these findings show that the aging brain

has preserved circuitry for allocating attention to information that it finds evocative and homeostatically important, even if the circuitry for allocating attention to information on a cognitive basis is diminished with age.

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Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

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Program#/Poster#: 622.19/Y11

Topic: F.01. Human Cognition and Behavior

Support: AG038490

Title: Neural mechanisms supporting successful speech comprehension in normal aging

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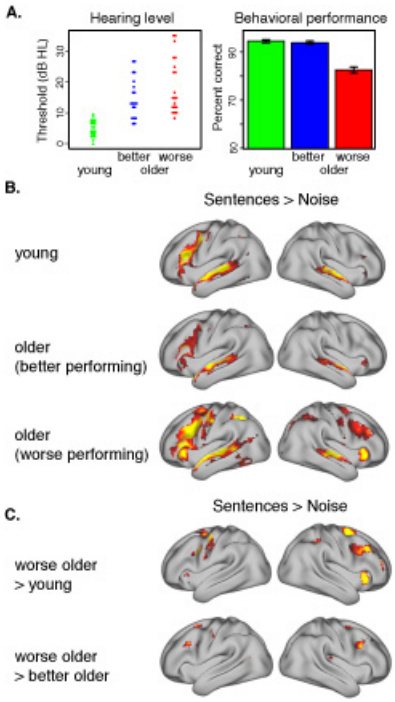
Abstract: Although declines in hearing ability typically occur during normal aging, many older adults retain high levels of speech comprehension ability. However, older listeners differ in their degree of success, and the reasons for this variability are unclear. In the present fMRI study we recruited a group of 39 older adult listeners (mean age=65.9 years). Participants underwent scanning while listening to sentences varying in both syntactic complexity (subject-relative vs. object-relative embedded clause) and acoustic richness (acoustically rich vs. acoustically degraded using noise vocoding). For each sentence, participants indicated the gender of the character performing the action via button press. We split the older adults into better-performing (n=19) and worse-performing groups (n=20) based on their behavioral performance. The better performing older adults show accuracy scores and reaction times comparable to those of the young adults (n=26). Hearing acuity is well matched across the two groups of older subjects, while significantly worse than that of young adults (Figure 1A). Neural activity for these groups of subjects is shown in Figure1B. The good-performing older adults show activity that is statistically indistinguishable from the young adults. By contrast, the poor-performing older

adults show increased activity in frontal cortex and cerebellum compared to their good-performing counterparts. Because these patterns of activity were associated with correct responses, we conclude that these additional regions are recruited to maintain high levels of speech comprehension in the poor-performing older group (Figure 1C). Taken together, our findings demonstrate more dynamic interplay of task demands, neural recruitment, and behavioral performance during spoken language comprehension.



Disclosures: **Y.-. Lee:** None. **C. Rogers:** None. **N. Min:** None. **A. Wingfield:** None. **M. Grossman:** None. **J. Peelle:** None.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

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Title: Age-dependent community dynamics and brain system organization in human functional brain networks

Authors: *K. J. SCHLESINGER[1], B. O. TURNER[2], B. LOPEZ[2], M. B. MILLER[2], J. M. CARLSON[1];
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Abstract: As humans age, cognition and behavior change significantly, along with associated brain function and organization. Aging has been shown to decrease variability in functional magnetic resonance imaging (fMRI) signals [1], and to affect the modular organization of human brain function [2]. In this work, we use complex network analysis to investigate the dynamic community structure of large-scale brain function, asking how evolving communities interact with known functional systems, and whether the dynamics of communities and brain systems are affected by age. We analyze networks derived from fMRI scans of 105 human subjects (53 female; not analyzed separately by sex) performing a word memory task. Network nodes are 94 anatomical brain regions, and dynamic edge weights are defined as the low-frequency (0.06-0.125 Hz) wavelet coherence of activity between pairs of nodes, computed within each of a set of sequential time windows. We determine the time-evolving modular structure of these networks by maximizing the multislice modularity [3], thereby identifying distinct communities, or sets of brain regions with strong intra-set functional coherence. To describe changes in community structure over time, we use flexibility, or the probability that brain regions will switch between communities [4]. We find a significant positive correlation between age and flexibility: brain regions of younger subjects tend to change communities less often during the memory task. We characterize the relationship of community structure to known brain systems by the recruitment coefficient, or the probability of a brain region being grouped in the same community as other regions in the same system [5]. We find that subcortical regions and regions associated with fronto-parietal and cingulo-opercular circuits have a significantly higher recruitment coefficient in younger subjects. This indicates that the within-system functional coherence of these specific systems during the memory task declines with age; such a correspondence does not exist for other systems (e.g. visual and dorsal attention), whose recruitment coefficients remain relatively uniform across ages. These results confirm that the dynamics of functional community structure vary with age, and demonstrate methods for investigating how aging differentially impacts the functional organization of different brain systems. [1] D.D. Garrett et al. J Neurosci. 2011; 31(12): 4496-503. [2] D. Meunier et al. NeuroImage 2009; 44(3): 715-23. [3] P.J. Mucha et al. Science 2010; 328: 876-8. [4] D.S. Bassett et al. PNAS 2011; 108(18): 7641-6. [5] D.S. Bassett et al. Network Community Toolbox. commdetect.weebly.com.

Disclosures: **K.J. Schlesinger:** None. **B.O. Turner:** None. **B. Lopez:** None. **M.B. Miller:** None. **J.M. Carlson:** None.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

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Evelyn F. McKnight Brain Institute

Title: Gray matter volumes related to body fat predict executive functions differentially in males and females

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Abstract: Obesity is associated with brain structure and cognitive functioning in some studies but not others. Typical measures of obesity, like body mass index, may be limited in their ability to operationalize body fat, especially in males and older adults. The current study investigated the impact of percent body fat, measured with an impedance scale, on brain structure and executive functioning and sought to determine if there were different impacts on males versus females. Males (n = 18) and females (n = 18), ages 60-80, were matched on age, education, and hypertensive status. Voxel-based morphometry was used to identify gray and white matter regions that decreased as percent body fat increased ($p < .001$), controlling for age, intracranial volume, and gender. Decreasing gray matter regions included bilateral fusiform, right medial temporal, left occipital, bilateral parietal, left cingulate, and left middle frontal areas. White matter volumes decreased in the left occipital, left medial temporal, and right parietal regions as percent body fat increased. Volumes were extracted from each significant cluster to create regions of interest (ROIs). ROIs were residualized to take into account the effects of age and intracranial volume. Separate univariate general linear models were used to predict executive function tasks (Global-Local, Stroop, and Keep Track tasks) from ROIs, gender, and the interaction between ROIs and gender. In males higher gray matter volumes in the left occipital lobe were associated with better performance on the Keep Track Task but were not associated in females. In females, but not males, better performance on the Stroop was associated with higher

volumes in the left cingulate and the right parietal lobe. No associations were found for white matter volumes. Results suggest that higher body fat may be affecting different aspects of cognition for males versus females.

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Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

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Support: NSERC ENGAGE EGP470367-14

Title: Characterizing population EEG dynamics throughout adulthood

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Abstract: For decades, electroencephalography (EEG) has been a useful tool for investigating the underlying neural mechanisms of human psychological processes. However, traditional laboratory investigations are limited by the time-consuming nature of running human EEG studies, which constrains the numbers of participants included in most studies. Using InteraXon's Muse, a portable and wireless 4-channel EEG headband, we obtained EEG recordings from 6029 (1650 women) consenting users worldwide who ranged from 18 to 88 years in age (M = 41.7 years old, SD = 13.0) while users completed a category exemplar task followed by a mindfulness-based stress reduction exercise. Here, we report age-related changes in EEG power at a very fine chronological scale. EEG was recorded from prefrontal and temporoparietal locations in each hemisphere while users completed a one-minute category exemplar task followed by a three to 20-minute session of a mindfulness-based stress reduction exercise. Because some participants had completed hundreds of sessions, our initial analyses were limited to just five sessions per unique user, to avoid overrepresentation of single users. All artifact-free EEG data from each prefrontal and temporoparietal electrode site were subjected to a Fourier transform to yield estimates of EEG power in five traditional frequency bands (delta, theta, alpha, beta, and gamma). We also calculated the peak alpha frequency at temporoparietal

sites, and separate alpha asymmetry measures for the prefrontal and temporoparietal sites. We found that EEG power changed as a function of age depending on sex and frequency band. Prefrontal alpha and beta power increased with age, and overall EEG power increased more for women than men. We also found a gradual (year-by-year) slowing of the peak alpha frequency with increased age, for both sexes. Finally, our analysis of alpha asymmetry revealed a linear increase in right frontal activity (EEG alpha power is inversely related to activity) with age. Our results replicate a number of previous findings such as increased alpha power and slowing of the peak alpha frequency with age. We also found a shift towards greater relative right frontal EEG activity with age, possibly reflecting a bias toward negative affect. Unlike previous age-related EEG studies which have been limited by sample size and restricted age ranges, our work highlights the advantage of using "Big Data" to address questions about developmental brain changes with large and representative samples. Findings are also discussed in terms of their relevance to brain-based models of emotional well-being and illness related to aging.

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Poster

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Topic: F.01. Human Cognition and Behavior

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Title: Dual-task functional connectivity changes induced by exercise in the elderly

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Abstract: While physical training seems to affect only some cognitive tasks on elderly people, its influence is explained via changes in intrinsic or task-independent resting state functional connectivities (FC) (1, 2, 3). In contrast, we use a Bayesian network algorithm to examine the change in dual-task (DT) FC of 55 healthy seniors (mean age = 66.6 ± 6.7) as they discriminate

letters and/or numbers (details in 4) at before and after 6 months of exercise training. Mean response time of DT is significantly improved after exercise training (p=.012) (Fig. 1). We use a high-level generalized linear model to find DT activated regions within frontal, temporal and parietal areas (5, 6, 7). The identified regions are then considered as nodes of the graphical model analysis. fMRI time series at those nodes are fed into IMaGES (8) to determine inter-region FC during DT processing. This step is done separately for the fMRI data collected on the same set of regions before and after the exercise intervention. Thus, by comparing the two networks, we can observe exercise training-induced FC changes (Fig. 2). After 6-months of exercise training, inter-hemisphere connectivity appears between left and right pars opercularis in the Broca's area. Given that DT performance suffers greatly by age (9), this exercise-induced FC likely helps to compensate for neural deficiency by employing homologous contralateral regions (10) and thus boosting the performance. Furthermore, there appear two more FC within the fronto-parietal network - a core of task initiation and coordination (11, 6). Given the age-related connectivity disruptions (12, 13), these newly exercise-induced FC may support significant improvement in DT performance after 6 months of exercise via an increased number of connections. Future analysis will include the 3rd data sets acquired after 12 months of exercise. The 6-month and 12-month induced FC connective strength will be related to corresponding DT improvements. This analysis will provide further insight into the neural mechanism through which exercise training can positively affect DT performance.

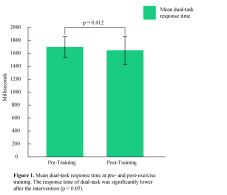

Figure 1. Mean dual-task response time at pre- and post-exercise training. The response time of dual-task was significantly lower after the intervention ($p < 0.05$).

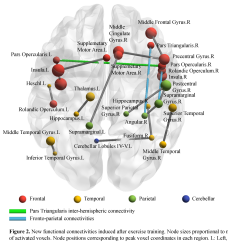

Figure 2. New functional connectivities induced after exercise training. Node sizes proportional to number of activated voxels. Node positions corresponding to peak voxel coordinates in each region. L: Left, R: Right.

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Disclosures: L.T.K. Vo: None. **M.N.N. To:** None. **A.F. Kramer:** None.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 622.24/Y16

Topic: F.01. Human Cognition and Behavior

Support: VA CSRD . 5I01CX000501

ADNI U01 AG024904

Title: Brain metabolism, amyloid, vascular disease: anterior cingulate cortex and cognitive aging

Authors: *J. V. PARDO[1], J. T. LEE[2];
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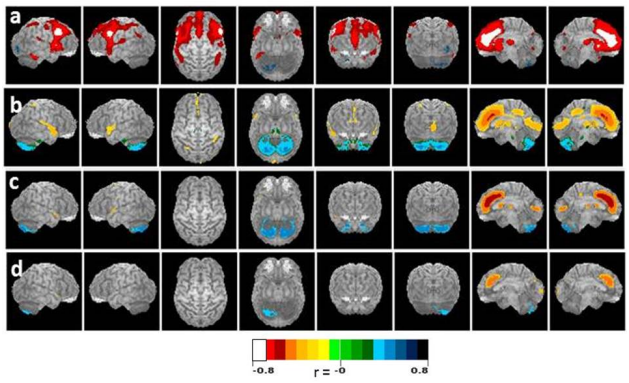
Abstract: The anterior cingulate cortex (ACC) is a critical nexus for declining glucose metabolism during healthy aging. The decline in glucose metabolism correlates with age-associated decline in cognitive function particularly executive functions. Healthy elders from the ADNI database were examined for changes in brain metabolism, amyloid, and vascular disease risk (Hachinski, "Hach") that correlated with age. Data included FDG and amyloid PET both normalized to the cerebellum. The significance of voxel-wise, whole-brain, Z-scores was adjusted ($p < 0.05$) dividing by resels. Several comparisons are shown in the figure showing voxel-wise correlations with age: a) 46 healthy normals (18-90 y) reported in Pardo et al 2008 (*Neuroimage* 35:1231); b) 210 ADNI normal (age 56-90 years); c) 103 ADNI normal (56-90 y) Hach = 0; d) 107 ADNI normal (63-89 y) Hach = 1-3. For the ACC region, the correlation of metabolism with age was $r = -0.49$ ($p < 10^{-6}$), while for amyloid the correlation with age was $r = +0.01$ ($p = 0.88$). The robust decline in metabolism of the ACC with age was replicated in the ADNI dataset and occurred even in those without major vascular risk factors. ACC metabolism decreased at a much greater rate than did amyloid deposition. These findings suggest the need to consider alternative pathophysiological mechanisms for aging-associated ACC dysfunction.



Disclosures: **J.V. Pardo:** None. **J.T. Lee:** None.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 622.25/Y17

Topic: F.01. Human Cognition and Behavior

Title: Healthy children with Apolipoprotein E4 carriers showed a stronger connectivity between nodal regions of default mode networks that linked to weakened functional connections between hippocampus and default mode networks

Authors: *A. ARINO[1,2], M. ABE[2], D. MICHIMATA[1,2], S. YOKOTA[3], T. HASHIMOTO[3], K. FURUKAWA[4], M. KAMADA[4], H. ARAI[4], H. TAKEUCHI[2], R. KAWASHIMA[3], Y. TAKI[2]; [1]Fac. of Med., Tohoku Univ., Sendai-Shi, Japan; [2]Nuclear Med. and Radiology, [3]Inst. of Aging, Develop. and Cancer, Tohoku Univ., Sendai, Japan; [4]Geriatrics and Gerontology, Inst. of Development, Aging and Cancer, Sendai, Japan

Abstract: Apolipoprotein E epsilon4 allele (Apo E4) is an established genetic risk factor for late-onset Alzheimer's disease. It is known that Apo E4 proteins can modulate development and maturation of neural circuits in animal models. However, whether a genetic variant of Apo E4 allows organizing different brain networks in childhood in humans is unknown. Here, using functional magnetic resonance imaging (fMRI) techniques, we examined different interregional brain networks during rest, called resting networks, in healthy children with a genetic variant of Apo E4 (i.e. carriers, age 13.8 ± 2.5 n = 31 [male 19, female 12]) compared with age-matched, non-carrier children (age 13.8 ± 2.5, n = 31 [male 19, female 12]). We hypothesized that impaired functions of hippocampus in Apo E4 carriers would involve a compensatory overfunction of default mode networks that have known functionally declined in an early stage of late-onset Alzheimer's disease. Functional brain imaging was acquired while subjects were lying on a bed with their eyes open and were not engaged in any tasks in a 3 Tesla MRI scanner (Fillips, xxxxx). Wechsler Intelligence Scale for Children-Revised was also performed to ensure comparable IQ scores between the carries and noncarriers. Imaging data was realigned, normalized and smoothed with use of SPM (http://www.fil.ion.ucl.ac.uk/spm) in each subject. Functional connectivity between hippocampus and nodal regions of default mode networks, and between regions within default mode networks were computed in each subject using a simple regression model and then compared between carriers and noncarriers in group analysis. Our results revealed a stronger functional coupling between posterior cingulate cortex (PCC) and other nodal regions within default mode networks when functional connections between hippocampus and PCC showed weaker in carriers but not in noncarriers. Healthy children with

Apolipoprotein E4 carriers showed a stronger connectivity between nodal regions of default mode networks that linked to weakened functional connections between hippocampus and PCC.

Disclosures: **A. Arino:** None. **M. Abe:** None. **D. Michimata:** None. **S. Yokota:** None. **T. Hashimoto:** None. **K. Furukawa:** None. **M. Kamada:** None. **H. Arai:** None. **H. Takeuchi:** None. **R. Kawashima:** None. **Y. Taki:** None.

Poster

622. Changes of Functional Network Activity: Physiology, Normal Ageing and Neurodegenerative Disease

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 622.26/Y18

Topic: F.01. Human Cognition and Behavior

Support: NIH Grant 5R37AG-006265-25

Title: Evidence that decreased system segregation observed across the healthy adult lifespan does not result in differences in resting-state defined system topology

Authors: ***M. Y. CHAN**[1], F. ALHAZMI[1], N. K. SAVALIA[1], D. C. PARK[1,2], G. S. WIG[1,2]; [1]Ctr. for Vital Longevity and Sch. of Behavioral and Brain Sci., Univ. of Texas at Dallas, Dallas, TX; [2]Dept. of Psychiatry, Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Functional brain networks exhibit a modular organization in young adulthood. Modular organization is characterized by dense within-system connectivity and sparser between-system connectivity (i.e., the presence of segregated but not disconnected brain systems). Recent work from our laboratory has demonstrated that the segregation of brain systems decreases with increasing age, and that the degree of segregation in association systems predicts memory ability independent of age (Chan et al., 2014). While our initial report began to explore distinctions in segregation as a function of system type (sensory-motor vs. association), it was unclear how differences in segregation related to the connection patterns of specific nodes. Further, as decreasing system segregation reflects increases in connections between systems, it was also unclear how age-related differences in segregation influenced the overall network topology of functional systems across adulthood. We analyzed data from the Dallas Lifespan Brain Study (N=238; age: 20-89 years). Following thorough data cleaning and quality-control procedures, we analyzed participants' resting-state functional connectivity (RSFC) to both probe the source of age-related de-segregation on a node-level, and understand the community structure of functional systems across four different age groups (YA=20-34 years, ME=35-49 years, ML=50-64 years,

OA=65-89 years). Brain network nodes were defined with a biologically plausible parcellation of area features (Wig et al., 2014); edges were defined by the pairwise Fisher's z-transformed Pearson correlation between the average resting-state time series of every node with one another, in each participant. We found non-uniform increases in between-system connections in the nodes of both sensory-motor and association systems. Nodes with lesser connections to systems outside of their own in younger adults exhibited the greatest increases in between-system connections across older adulthood. We then examined the topology of functional brain systems as revealed by community detection algorithms. Despite the observed differences in patterns of connections across age, community-detection revealed that while minor shifts in community structure occur, most of the 'canonical' brain systems (e.g., frontal-parietal control, visual, default) are present across the healthy adult lifespan. These results serve to further illuminate our understanding of differences in segregation observed across healthy adulthood.

Disclosures: M.Y. Chan: None. **F. Alhazmi:** None. **N.K. Savalia:** None. **D.C. Park:** None. **G.S. Wig:** None.

Poster

623. Cognition and Anxiety: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 623.01/Y19

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: Department of Defense W81XWH-08-2-0110

The Dielmann Genetic and Environmental Risk Endowment

NIH grant MH072672

Title: Effect of chronic plus acute prolonged stress on expression of platelet derived growth factor in the rat orbitofrontal cortex

Authors: *K. SMITH[1], D. A. CRUZ[2], B. BINGHAM[2], R. R. BURSON[3], D. A. MORILAK[2], D. E. WILLIAMSON[2];
[1]UT Hlth. Sci. Ctr. San Antonio, San Antonio, TX; [2]Univ. of Texas Hlth. Sci. Ctr. San Antonio, San Antonio, TX; [3]San Antonio Military Med. Ctr., San Antonio, TX

Abstract: In a cohort of active military personnel, we have observed an increase in protein levels of platelet derived growth factor (PDGF) associated with prior deployment that is further elevated if they also have posttraumatic stress disorder (PTSD). In parallel, we have also

observed a significant decrease in DNA methylation and an increase in gene expression of the PDFGα receptor gene in the medial orbital frontal cortex (OFC) of human postmortem brain tissue in PTSD patients compared to controls. To further investigate how exposure to traumatic stress may underlie these differences, we utilized a rat preclinical model of PTSD, the Chronic plus Acute Prolonged Stress (CAPS) model, which induces PTSD-like behavioral changes. Groups of rats were first fear-conditioned to a tone and then subject to control or CAPS treatment (14 days cold stress, 4°C 6 hr/day, then 3 acute stressors on day 15). We then examined mRNA levels of PDGF ligands (A,B,C, and D) and their receptors (α and β) in the OFC on day 21 following extinction retention testing in one group, and following two days of rest in the home cage in another group. In animals that were exposed to CAPS without fear extinction training, we observed significantly lower mRNA levels in CAPS treated rats for both PDGF α ($p<.05$) and β ($p<.01$) receptors but no differences between the groups for any of the four PDGF ligands. In the group that received fear extinction training, there was no difference in mRNA expression of either receptor between the CAPS treated and control rats, however, mRNA levels of PDGF C were decreased in CAPS treated rats compared to controls ($p<.02$). These preliminary results suggest that CAPS treatment following fear conditioning reduces the expression of the PDGF α and β receptors in the OFC of rats, and that this difference is not seen following fear extinction. Our data could serve as a model to investigate the importance of this gene in fear learning and how it may contribute to changes induced by behavioral interventions, such as exposure therapy. Understanding the convergence of gene expression in clinical PTSD and preclinical models of fear conditioning and extinction will ultimately aid in uncovering the root causes of this debilitating condition.

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Poster

623. Cognition and Anxiety: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 623.02/Y20

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: KAKENHI (221S0003)

RIKEN NIJC

Title: Effect of time-of-day on mouse behavior measured in a comprehensive behavioral test battery

Authors: *K. TAKAO[1], H. SHOJI[2], S. HATTORI[2], T. MIYAKAWA[2,1];
[1]Natl. Inst. For Physiological Sci., Okazaki, Japan; [2]Fujita Hlth. Univ., Toyoake, Japan

Abstract: Mouse behavior is analyzed in laboratories to elucidate the effects of various experimental manipulations, including gene mutation and drug administration. When the effect of a factor (manipulation) of interest is assessed, other factors, such as age, sex, temperature, apparatus, housing, etc., are controlled for in the experiments by matching, counterbalancing, and/or randomizing. One of such factors that has not received much attention is the effect of time-of-day when the mice are subjected to the tests. Here we evaluated the effects of time-of-day on mice behaviors by analyzing the combined data of approximately 2000 C57BL/6J mice that we collected using our comprehensive behavioral test battery including the light/dark transition test, open field test, elevated plus maze, hot plate test, social interaction test rotarod test, prepulse inhibition, Porsolt forced swim test, tail suspension test, cued and contextual fear conditioning test, and 24-hour homecage activity monitoring test. The mice were maintained under a 12-h light:12-h dark cycle (lights on at 7:00), and subjected to the tests included in the battery from 9:00 to 18:00, during the light phase. Locomotor activity in the open field test, pain sensitivity in the hotplate test, anxiety-like behavior in the light/dark transition test, and prepulse inhibition of acoustic startle response were significantly influenced by time-of-day of testing. On the other hand, we failed to detect significant effects of time-of-day of testing on the results of the elevated plus maze test, social interaction test, Porsolt forced swimming test, tail suspension test, or cued and contextual fear conditioning test, except for some indices related to locomotor activity in these tests. The results of the present study suggest that time-of-day of testing affects locomotor activity, a certain type of anxiety-like behavior, pain sensitivity, and prepulse inhibition in mice. Thus, the time-of-day of testing should be carefully counterbalanced between groups to be compared in behavioral tests.

Disclosures: **K. Takao:** None. **H. Shoji:** None. **S. Hattori:** None. **T. Miyakawa:** None.

Poster

623. Cognition and Anxiety: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 623.03/Y21

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Study of anxiolytic effects of kami kihi to (gui pi tang) in rats

Authors: J. V. CIANCAGLINI, Jr[1], *B. B. SILVA[1], M. POLLY, Jr[1], R. S. DE LIMA, jr[1], F. S. GUIMARÃES, Jr[1], P. L. LANNI, Jr[2], L. C. D. NETO, Jr[1], D. FEDER, Dr[2], C. D. NASSIS, Dr[3]; [2]Farmacologia, [3]Famarcologia, [1]Faculdade De Medicina Do ABC, Santo Andre, Brazil

Abstract: INTRODUCTION: Kami-kihi-to (KKT, gui pi tang) is a medicinal herbal mixture used in traditional japanese and chinese medicines. Some of its components like ginseng, astragalus, longan (Longanae arillus), angelica and polygata have proved therapeutic effects in the treatment of central nervous system disordes. KKT has been prescribed by traditional oriental medicine phisicians to treat anxiety, but this use lacks experimental validation. In addition to being effective for central nervous system disorders (such as amnesia and cognitive disturbances of learning and memory), the KKT has proven an effective anxiolytic. Previous studies have shown that after anxiogenic induction by the use of reverse agonist of benzodizepine in animals, the gui-pi-tang proved to be a competent anxiolytic (per share antagonist to benzodiazepine receptors) when compared to a benzodizepine agonist (diazepam). OBJECTIVES: Experimental validation of the traditional use of KKT in anxious diseases and the comparison between eventual kkt effects to fluoxetine effects on anxiety. MATERIAL AND METHODS: 30 Wistar male rats were divided in 3 groups (n=10) and received, for 21 days, orally, the following treatment: group A (control): 0,5ml saline/day; group B: fluoxetine 10mg/kg/day; group C: KKT (aqueous extract) 1,66 ml/kg/day. In the 22nd day animals were submitted to elevated T maze, and withdrawal (WL) and escape (EL) latency times (s) were assessed to each group. In the first step (WL), animals were placed on the distal end of the maze closed, and the time took for each animal to get out of that arm with the four paws was assessed. In the second step (EL), each animal was placed on the end of the maze's open arm and the time measures were carried out like the ones made in the first step. Results intergroups were compared by means of variance analysis (p</= 0,05) and Kruskal Wallis test. RESULTS (mean of each group +/- sdm): WL: A 250,17 +/- 86,52 ; B 137,7 +/-75,50* ; C 241,26 +/-89,2. EL: A 194,72 +/-125,1 ; B 19,1 +/-12,91* ; C 115,36 +/-113,27 . * = statistic significance (p</= 0,05) when compared to control group. Reduction of withdrawal time can be related to an anxiolytic effect on generalized anxiety disease (GAD), while reduction of escape time indicates a panicolytic effect. Fluoxetine, has both of these effects, and our results did confirm it. KKT, however, did not show any significant effect on withdrawal or escape latency times. CONCLUSION: KKT treatment, in rats, did not show any significant effect on anxious behaviors of rats submitted to elevated T maze. Our results, therefore, do not support the traditional use of KKT on anxiety.

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Poster

623. Cognition and Anxiety: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 623.04/Y22

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Effects of Lippia alba on animals submitted to the elevated t-maze test

Authors: *J. E. PANDOSSIO, N. M. MARTINS, P. M. MARTINS;
Univ. of Brasilia, Brasília, Brazil

Abstract: Anxiety disorders represent prevalent psychiatric condition in clinical practice and are associated with important social and functional impairment, comorbidity, disability and reduced quality of life. Among the theories proposed to explain the neurobiology of anxiety disorders, it is highlighted the dual role of serotonin (5-HT), based on the mechanism of action of drugs that act on serotonergic neurotransmission. In spite of the clinic pharmacological options available, only a small number of patients has adequate response to treatment. Therefore, new therapeutic approaches can ensure higher response rates, greater therapeutic adherence, with lower losses associated with these disorders. In this sense, Lippia alba (L. alba), a plant species widely used in folk medicine, has been investigated as to their anxiolytic properties. Thus, it was intended to evaluate the effects of aqueous extract of L. alba on the behavior of animals submitted to the elevated T-maze model (ETM). Female Wistar rats (n = 58) were divided in the groups saline, fluoxetine, buspirone, flurazepam (controls) and extracts of L. alba at doses of 25, 50 and 75mg/kg (experimental groups), all with intraperitoneal administration, in order to verify the latency of inhibitory avoidance and escape, with three trials each. After the ETM, it was verified, in the open field, the frequencies of crossings, rearings and grooming, evaluating the possibility of sedation in this model. The ANOVA one-way repeated measures, followed by Student Newman-Keuls test showed that treatment with the extract of L. alba facilitated inhibitory avoidance (anxiogenic effect) and impaired escape (panicolytic effect) in ETM, specially at doses of 50 for escape ($F(2,6) = 5,35$; $p = 0,02$) and 75mg/kg for avoidance ($F(2,8) = 23,74$; $p = 0,00003$) and escape ($F(2,8) = 4,40$; $p = 0,03$), compared with controls. In the open field it was not observed induction of sedation by any plant doses. These observations suggest that the extract of L. alba can exert anxiolytic effect on a set of defensive behaviors implicated in panic, but not on generalized anxiety, resembling found for buspirone, a drug that acts selectively on 5-HT1A receptors, possibly implying the involvement of serotonergic neurotransmission.

Disclosures: J.E. Pandossio: None. **N.M. Martins:** None. **P.M. Martins:** None.

Poster

623. Cognition and Anxiety: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 623.05/Y23

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: a grant-in-aid for general scientific research from the Ministry of Education,Science,and Culture of Japan

a grant from Strategic Research Program for Brain of the Ministry of Education, Culture, Sports, Science and Technology of Japan

Title: Hippocampal abnormalities through the activation of glucocorticoid receptor in the hippocampus of an animal model of PTSD

Authors: N. NAGASHIMA[1], *M. FUCHIKAMI[1], S. NOJIMA[2], T. KATAOKA[1], S. OKADA[1], H. TAKEMOTO[3], S. MORINOBU[4], S. YAMAWAKI[1];
[1]Hiroshima University, Dept. of Psychiatry, Hiroshima, Hiroshima, Japan; [2]Natl. Hosp. Organization, Kamo Mental Hlth. Ctr., Higashihiroshima, Hiroshima, Japan; [3]Prefectulal Univ. of hiroshima, Dept. of Preservation of health welfare science, Mihara, Hiroshima, Japan; [4]Kochi Med. School, Kochi University, Dept. of Neuropsychiatry, Nankoku, Kochi, Japan

Abstract: Posttraumatic stress disorder (PTSD), a complex disorder associated with an intricate biological and psychological symptom profile, is induced by exposure to life-threatening trauma. Although the detailed mechanisms are not fully uncovered, results of the clinical studies of PTSD, such as the enhanced negative feedback of the hypothalamo-pituitary-adrenal axis, hippocampal atrophy, and fear memory extinction, suggest the functional as well as morphological abnormalities in the hippocampus in response to severe stress are closely involved in the pathophysiology of this disorder. In this context, it is important to examine the alteration of hippocampal gene expression through glucocorticoid receptor (GR) in an animal model of PTSD to elucidate the pathophysiology of PTSD. In a series of studies, we validated the single prolonged stress (SPS) as a model for PTSD. So, we first examined whether SPS changed the nuclear levels of GR in the rat hippocampus 1, 2, 4, 24 hours and 7days after the exposure to SPS by using Western blot. Nuclear levels of GR were significantly increased 1, and 2 h after SPS, suggesting that the transcription of gene expression mediated by glucocorticoid response element (GRE) may be activated. In second, we are examining the GR binding to the GRE at the promoter of the Bcl-2 and Bax gene by ChIP-qPCR assay. Simultaneously, we examined the spine abnormalities of the CA1 and CA3 pyramidal cells in the hippocampus of SPS rats by Golgi staining. There were no changes in the length and density of spine in CA1 or CA3 region, but a significant decrease in the diameter of spine was found in CA1 pyramidal cells. In addition,

we will demonstrate the involvement of apoptotic pathway in the spine abnormalities in the hippocampus of SPS rats.

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Poster

623. Cognition and Anxiety: Animal Models

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Program#/Poster#: 623.06/Y24

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NIH-ENDURE 2-R25NS080687-06

Title: Modulation of the Endocannabinoid System within the Nucleus Accumbens shell elicits anxiolytic effects in rats

Authors: T. PARDO-GARCÍA[1], N. YUSIF[2], *C. S. MALDONADO-VLAAR[3];
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Abstract: Preclinical investigations have demonstrated that the endocannabinoids and its receptor CB1 can modulate emotional responses. In addition, studies point to a modulatory role of the transient receptor potential vanilloid 1(TRPV1) within the brain endocannabinoid system. In mice, previous immunocytochemical findings reported a high density of co-localized CB1 and TRPV1 receptors within the NAc shell. In addition, the NAc shell is found to also regulate anxiogenic responses in animal models. To our knowledge, the functional role of the co-localization of the CB1 endocannabinoid receptor and (TRPV1) receptor within the Nucleus Accumbens (NAc) has not been studied. Thus, the present study seeks to elucidate the effects of this receptor interaction within NAc Shell subregion on anxiety states. We hypothesized that blockade of this interaction within the NAc shell will elicit and anxiolytic response in rats. In order to test our hypothesis we conducted the present experiment in which male Sprague Dawley rats were implanted with bilateral brain cannulae aimed at the NAc shell. Following recovery from surgery, animals received pre-treatment of microinfusions (0, 0.125, 0.25 nmol/0.4µl) of N-arachidonoyl-serotonin (AA-5-HT), a dual blocker of the endocannabinoid-inactivating enzyme, fatty acid amide hydrolase (FAAH) and a TRPV1 antagonist, within the Nac shell. After the treatment, animals were tested in an elevated plus maze paradigm for a period of 5 minutes. Behavioral parameters measured were: Time Spent in Open Arms, Time Spent in Closed Arms, Rearing, Flatback and Grooming. At the end of the experiment, animals were sacrificed and their

brains collected for histological analysis. Results showed that the pre-treatment with the antagonist significantly increased the time spent in the open arms in animals compared to vehicle injections ($p < 0.0005$). Significant differences were also found in time spent in closed arms and grooming parameters following antagonist treatment. The present findings suggest that the endocannabinoid system modulates anxiety within the NAc shell and that co-localization of CB1 and TRPV1 receptors may play a role in mediating emotional responses.

Disclosures: **T. Pardo-García:** None. **N. Yusif:** None. **C.S. Maldonado-Vlaar:** None.

Poster

623. Cognition and Anxiety: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 623.07/Y25

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: VA Merit Award BX002558-01

Title: Effect of COMTval158met polymorphism on sensitivity to long-term effects of trauma in the predator stress model of PTSD

Authors: ***J. DESLAURIERS**[1,2], M. TOTH[1,2], D. HOPPENER[3], M. A. GEYER[1,2], V. B. RISBROUGH[1,2];
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Abstract: Posttraumatic stress disorder (PTSD) affects 7-8% of the American population while rates are up to 20% in military veterans. The val158met polymorphism in the COMT gene has been associated with a greater risk of neuropsychiatric disorders, including PTSD. Our hypothesis is that the COMTval158met polymorphism modulates the response to a severe trauma, increasing the risk to develop a PTSD-like phenotype. To test this hypothesis we examined the sensitivity of mice “humanized” for the COMTval158 to the predator stress model of PTSD. Our previous studies suggest that this mouse line has similar cognitive phenotypes as reported in human COMTval158met carriers, with Met/Met mice exhibiting increased working memory, sensorimotor gating and reduced fear extinction compared to Val/Val littermates. In the current study male and female Val/Val or Met/Met carriers were grouped into stress or control groups, with stressed groups being exposed to a cat for 10 minutes while control mice were handled, but were not exposed to the cat. One week after the predator stress, avoidance behaviors

(open field; light/dark box) were evaluated. Two weeks after the predator stress, mice were underwent a ”trauma-reminder test” in which their avoidance of cat litter was assessed. A composite avoidance score (average of Z-scores across the 3 tests) was calculated for each animal, with negative scores reflecting greater avoidance behavior. Overall, male Val/Val mice exhibited a decreased Z score, (i.e. increased avoidance behavior) compared to Met/Met mice, suggesting baseline anxiety differences across Val and Met carriers. Predator stress also significantly decreased Z scores, resulting in the greatest avoidance behavior being in the Val/Val-stressed mice. In females, there was a significant robust effect of predator stress regardless of COMT genotype, which may have resulted in ceiling effects. These results suggest that the COMTval158met polymorphism modulates the response to a severe trauma in males, here mimicked by the predator stress, and support the double-hit hypothesis of PTSD. This two-hit model may be useful to understand the mechanisms implicated in the risk for development of PTSD-like symptoms. Results from a second experiment using a milder form of predator stress (no physical contact), will also be presented.

Disclosures: **J. Deslauriers:** None. **M. Toth:** None. **D. Hoppener:** None. **M.A. Geyer:** None. **V.B. Risbrough:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Johnson and Johnson.

Poster

623. Cognition and Anxiety: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 623.08/Y26

Topic: F.03. Motivation and Emotion

Title: Altered cognitive and motivational nociceptive processing in an animal model of post-traumatic stress disorder

Authors: ***J. D. VEGA-TORRES**, P. KALYAN-MASIH, T. HEERS, J. D. FIGUEROA; Basic Sci., Loma Linda Univ. Sch. of Med., Loma Linda, CA

Abstract: The nature of recent conflicts in Iraq and Afghanistan has resulted in a higher prevalence of comorbid chronic pain (CP) and post-traumatic stress disorder (PTSD) in veterans of Operations Enduring Freedom and Iraqi Freedom (OEF/OIF). Treatment of comorbid CP and PTSD remains a major challenge, as patients who suffer from both CP and PTSD experience greater pain, affective distress, and disability than patients with either condition alone. However, preclinical studies delineating the shared neurobiology of comorbid CP and PTSD are lacking.

This study was designed to investigate co-occurring pain-like and PTSD-like behaviors in a well-established predatory threat model of PTSD. Lewis rats (post-natal day 57-62) were placed on soiled cat litter for 10 min in a standard plastic mouse cage. Pain-related behaviors were assessed using both thermal (Hargreaves) and mechanical (von Frey) evoked reflex responses and a novel operant mechanical conflict-avoidance test (MCS). The responses of animals in both the elevated plus maze (EPM) and the acoustic startle response (ASR) tests served as tools for classifying rats as exhibiting PTSD-like behaviors. Testing sessions were performed one-week before (baseline) and one-week after exposure to predatory threat stress. Markers of neuroinflammatory activation (GFAP, Iba-1) were investigated in the thalamus and spinal cord using immunohistochemistry and Western blot. We found that animals exhibiting PTSD-like behaviors showed significant alterations in cognitive and motivational aspects of pain-like behaviors when compared to baseline responses ($p = 0.0022$). No significant differences were observed in thermal and mechanical evoked reflexes ($p > 0.05$). Interestingly, these behavioral results were not correlated with changes in the expression of astrocytes or microglia astrocyte assessed by glial fibrillary acidic protein and ionized calcium-binding adapter molecule immunohistochemistry. Together, our data demonstrates impairments in motivational nociceptive processing in PTSD-like rats, thus providing a useful model for elucidating supraspinal mechanisms and investigating potential treatments for comorbid chronic pain and PTSD.

Disclosures: J.D. Vega-Torres: None. **P. Kalyan-Masih:** None. **T. Heers:** None. **J.D. Figueroa:** None.

Poster

623. Cognition and Anxiety: Animal Models

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 623.09/Y27

Topic: F.03. Motivation and Emotion

Support: ERC-StG 312511

Title: Effects of familiarity on emotional contagion in rodents

Authors: *M. C. CARRILLO[1], F. MIGLIORATI[2], R. BRULS[2], T. VAN LIERDE[3], Y. HAN[2], M. HEINEMANS[4], I. PRUIS[4], V. GAZZOLA[2], C. KEYSERS[2];
[1]Social brain lab, Netherlands Inst. For Neurosci., Amsterdam Zuidoost, Netherlands; [2]Netherlands Inst. for Neurosci., Amsterdam, Netherlands; [3]Univ. Gent, Gent, Belgium; [4]Univ. of amsterdam, Amsterdam, Netherlands

Abstract: Witnessing of conspecifics in pain has been shown to elicit vicarious freezing in rodents. To date, however, it is unknown how the vicarious response is modulated by repeated exposure to a conspecific experiencing painful stimuli. A series of experiments were conducted in long Evans rats to investigate: 1) how the affective response of observers is modulated in a repeated witnessing paradigm, and 2) the role of familiarity in such paradigms. For the repeated witnessing experiments, shock-experienced observer rats repeatedly witnessed (6 times) familiar demonstrators experience painful footshocks. For experiments examining the role of familiarity, observer-demonstrator pairs were subdivided into 4 conditions: unfamiliar or familiar for either 1, 3 or 5 weeks by testing day. Familiarity was examinedfollowing a single or repeated witnessing of demonstrators experiencing painful footshocks. The results showed that vicarious freezing levels were gradually reduced as the tests progressed, reaching minimallevels by test 6. In contrast, the appearance and increase in the frequency of yawning, as the tests progressed, the fact that yawning mainly occurred during the shock period and that only observers expressed this behavior suggest that yawning was related to the distress of the demonstrators. This indicates that although vicarious freezing levels were reduced, perhaps, rats still share the emotional state of the other but they modify the expression. Moreover, results from the familiarity studies showed that in rats, the level of familiarity between the observer and demonstrator doesn't appear to modulate the vicarious response. Given, that familiarity between the observer and the demonstrator has been identified as a key modulator of the vicarious freezing response in mice, it is possible that the differences in the natural social structure between mice and rats determines its effect in the vicarious response.

Disclosures: M.C. Carrillo: None. **F. Migliorati:** None. **R. Bruls:** None. **T. van Lierde:** None. **Y. Han:** None. **M. heinemans:** None. **I. Pruis:** None. **V. Gazzola:** None. **C. Keysers:** None.

Poster

623. Cognition and Anxiety: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 623.10/Y28

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: DA033526 (EHC)

Title: Sex differences in kappa opioid receptor-mediated negative affective states in rats

Authors: *M. MAVRIKAKI, J. MAYS, D. PUTTICK, E. CHARTOFF;
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Abstract: Dynorphin, an endogenous ligand at kappa opioid receptors (KOR), is required for the expression of stress-induced depressive-like states in male rats. Previously we demonstrated that female rats are less sensitive to the depressive-like effects of KOR activation in the intracranial self-stimulation (ICSS) paradigm. The present study was designed to assess the role of KORs in the ability of an ethologically relevant stressor, social isolation (SI), to produce negative affective states in male and female rats. Adult male and female rats were either group housed (GH) or socially isolated (SI) for 5 weeks. The elevated plus maze (EPM) was used to assess the effects of SI on anxiety-like behavior. Place conditioning was used to assess the effects of SI on the aversive effects of the KOR agonist U50,488. In separate rats, effects of SI on brain region-specific levels of dynorphin and KOR mRNA expression were measured. SI reduced the amount of time spent in the open arms of the EPM in males but not females, suggesting that SI stress during adulthood produces greater anxiogenic effects in males. Female rats exposed to SI were less sensitive than males to U50,488-induced conditioned place aversions. Finally, levels of KOR mRNA in the bed nucleus of the stria terminalis (BNST), a brain region critical for anxiety-like behavior, depended on sex and housing condition: GH females had less, whereas SI females had more, KOR mRNA than similarly housed males. Our results are consistent with previous work demonstrating depressive-like effects of SI in males and they suggest that SI acts to modulate sensitivity to the anxiogenic effects of KOR activation through regulation of KOR levels in the BNST. Taken together, our findings raise the possibility that KOR ligands could be effective, gender-specific pharmacotherapies for anxiety and depressive disorders.

Disclosures: **M. Mavrikaki:** None. **J. Mays:** None. **D. Puttick:** None. **E. Chartoff:** None.

Poster

623. Cognition and Anxiety: Animal Models

Location: Hall A

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Program#/Poster#: 623.11/Y29

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Establishment of a behavioral-pharmacological evaluation on social interaction behavior using a 3-chamber system for rats

Authors: T. YAMAGUCHI[1], R. FUKUMORI[1], *M. YOSHIOKA[2], T. YAMAMOTO[1]; [1]Dept. of Pharmacol., Nagasaki Intl. Univ., Sasebo, Nagasaki, Japan; [2]Hokkaido Univ. Sch. Med., Sapporo, Hokkaido, Japan

Abstract: Social interaction test has been generally evaluated as index of social behaviors performed between two experimental animals. In this study, we established a new social

interaction test using a 3-chamber openfield system to examine the social behavior of rats. We used square-shaped openfield apparatus with 3-chamber system for social interaction test. A rat had been acclimated for 2 days in the openfield apparatus in which two stranger cages without rats were installed. After acclimation to the openfield apparatus, we measured the time required for the rat to approach the stranger cage in which a rat was placed by visual observation or video tracking analysis in the test trial. For measuring effects of lighting conditions, social behavior was examined under dark (5 lux) and bright conditions (350 lux). Under the dark condition, the time required for the rat to approach the stranger cage in which a rat was placed based on active contact was significantly longer than that measured under the bright condition, by visual observation. In addition, video tracking analysis using imaging data also showed a similar tendency. Briefly, this result was similar to that obtained by visual observation. In the social interaction test using the 3-chamber system, the time required for the rat to approach the stranger cage in which a rat was housed (social interaction time), which was measured by visual observation, was correlated with that by video tracking analysis. On the other hand, anxiolytics, tandospirone (3 mg/kg, i.p.) and diazepam (0.3 mg/kg, i.p.), significantly increased the time required to approach the stranger cage in which a rat was housed, without influencing spontaneous locomotor activity. In conclusion, this study revealed the behavioral-pharmacological validation of this social interaction test to evaluate innate anxiety and social behavior using a 3-chamber system in a single rat. In addition, this evaluation system may contribute to the elucidation of neural basis in social behaviors and the development of new therapeutic drugs for psychiatric diseases, including anxiolytics

Disclosures: **T. Yamaguchi:** None. **R. Fukumori:** None. **M. Yoshioka:** None. **T. Yamamoto:** None.

Poster

623. Cognition and Anxiety: Animal Models

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Program#/Poster#: 623.12/Y30

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Anxiolytic effect of Diferuloylmethane on rats exposed to ozone

Authors: ***L. HERNANDEZ**, J. J. RAMIREZ-VAZQUEZ, S. NERY-FLORES, G. CAMARGO, A. HERNANDEZ-CHAVEZ, M. MALDONADO-RUBIO, S. RAMOS CALZADA, M. L. MENDOZA-MAGAÑA, M. A. RAMIREZ HERRERA;
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Abstract: Background: Outdoor air pollution contains ozone, a pollutant that can harm our health when there are elevated levels in the air we breathe. High up in the atmosphere, ozone forms a layer that shields the Earth from ultraviolet rays. However, at ground level, ozone is considered a major air pollutant. This "bad" ozone is not emitted directly into the air, but is created by chemical reactions between oxides of nitrogen (NOx) and volatile organic compounds (VOC) in the presence of sunlight. Accumulating evidence suggests that outdoor air pollution may have a significant impact on central nervous system (CNS) health and dis ease. Particularly, short term ozone exposure in rodents has been reported to result in cerebral edema, neurodegeneration in the hippocampus, striatum, and substantia nigra, and altered behavior. A well-known damage mechanism of ozone is the oxidative stress and recently, oxidative stress has also been implicated in depression, anxiety disorders and high anxiety levels. In this work we explore the anxiety-like behavior in rats induced by ozone exposure and if this condition could be inhibited in rats treated with the phytochemical Diferuloylmethane (DFM), which has well documented antioxidant properties. Methods: 15 male Wistar rats (21-day old) housed in a standard 12::12 light-dark cycle and with ad libitum access to food and water, were divided in three study groups: an intact control group (CTL), a group of animals exposed during 15 days to ozone at 0.7 ppm for 4 h (OZO) and another group exposed to the same condition than OZO and fed with food supplemented with 5 mg/Kg/day Diferuloylmethane (OZO+DFM). All groups of rats were submitted to Force Swimming Test (FST) as described by Porsolt et al. Data was analyzed by one way Anova followed by the Dunnett`s test. The significance level was set at $p< 0.05$. Preliminary results and conclusions: OZO group shows a decrement of immobility time of 25% and an increment of climbing time to 110% in relation to CTRL group. OZO+DFM group only decrease 12% the immobility time and increase 24% the climbing time. These results suggest the Diferuloylmethane reduces the anxiety-like behavior induced by ozone exposure in rats.

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Poster

623. Cognition and Anxiety: Animal Models

Location: Hall A

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Program#/Poster#: 623.13/Y31

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: NIMHD P20MD002290

Title: Sex matters: Anxiolytic effects of diazepam and BDNF and parvalbumin protein levels

Authors: B. MASON[1], R. RAVENELLE[2], A. K. BERMAN[3], *S. DONALDSON[4];
[1]Developmental and Brain Sciences, Psychology, Univ. of Massachusetts Boston, Boston, MA; [2]CUNY Neurosci. Collaborative, City Univ. of New York, New York, NY; [3]Psychology, Western Michigan Univ., Kalamazoo, MI; [4]Univ. Massachusetts, Boston, Boston, MA

Abstract: In humans and animal models, those showing moderate to high anxiety-like behavior are more sensitive to anxiolytic drugs. In the present study, we examined whether there were any dose-dependent differences in the responses to diazepam (DZ: 0, 0.1 and 1.0 mg/kg, i.p.) in adult male and cycling female rats (tested while in proestrus, when estradiol (E2) was high) phenotyped as showing high- (HAn) and low anxiety (LAn)-like behavior. Further, we assessed parvalbumin (stains a subpopulation of GABA neurons) and brain-derived neurotrophin protein (BDNF) levels in forebrain and limbic structures implicated in anxiety/stress. At baseline, we saw significant differences between HAn and LAn animals, with HAn displaying less time on the open arms of the EPM, and less open arm entries, regardless of sex. Using three-week inter-trial intervals, we observed significant sex and trait differences in the anxiolytic effects of diazepam treatments on EPM, with proestrus, HAn females showing *less anxiety-like behavior* (ALB) at 0.1 mg/kg DZ and E2-rich LAn females displaying *less ALB* at 0.1 and 1.0 mg/kg DZ relative to males. Twenty-four hours after the completion of the DZ treatment, animals were sacrificed and brain tissue was harvested for immunohistochemistry analysis of protein levels of BDNF and parvalbumin in the medial prefrontal cortex (mPFC) and the hippocampus. BDNF protein was elevated in females and in the HAn line in mPFC, as was the number of PV immunoreactive cells (mPFC, CA2 and DG) relative to males from the same line. Taken together, our data demonstrate levels of estradiol influence ALB in the presence of the anxiolytic, diazepam, and that this may relate to increases in neuroplasticity and GABA neuron density in corticolimbic structures.

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Poster

623. Cognition and Anxiety: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 623.14/Y32

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Sex-dependent increase in myocardial sensitivity to ischemic injury in an animal model of post-traumatic stress disorder

Authors: *P. R. ZOLADZ[1], A. KRIVENKO[1], M. E. FRY[1], J. D. LAWSON[1], L. E. STONER[1], E. D. EISENMANN[1], B. L. JOHNSON[1], M. L. HEMBREE[1], R. M. ROSE[1], C. J. LOMBARDI[1], M. R. HUNTLEY[1], S. SEELEY[2], A. D. BUI[2], B. R. RORABAUGH[2];
[1]Psychology, Sociology, & Criminal Justice, [2]Pharmaceut. & Biomed. Sci., Ohio Northern Univ., Ada, OH

Abstract: Traumatized individuals who develop post-traumatic stress disorder (PTSD) are at increased risk for developing cardiovascular disease and exhibit greater mortality following cardiovascular-related events. Despite the link between PTSD and cardiovascular health, little work has examined the cardiovascular consequences of animal models of PTSD. Thus, in the present study, we examined the influence of a well-validated, psychosocial predator-based animal model of PTSD on myocardial sensitivity to ischemic injury. Male and female Sprague-Dawley rats were subjected to chronic psychosocial stress or control conditions for a period of 31 days. Rats in the psychosocial stress groups were given two 1-hr cat exposures, separated by a period of ten days, and experienced daily social instability throughout the experimental timeline. Rats in the control (no stress) groups were handled briefly each day and remained with the same cage mates throughout the 31-day period. On Day 32, anxiety-like behavior in the rats was assessed on the elevated plus maze, and on Day 33, rat hearts were isolated and subjected to 20 min ischemia and 2 hr reperfusion on a Langendorff isolated heart system. Psychosocial stress had no effect on pre-ischemic contractile function. However, post-ischemic recovery of rate pressure product and +dP/dT were attenuated in hearts from psychosocially stressed male, but not female, rats. In addition, psychosocial stress led to greater post-ischemic diastolic blood pressure and larger infarct sizes in male rats. These findings are the first to demonstrate increased myocardial sensitivity to ischemic injury in an animal model of PTSD and suggest that such effects are more pronounced in males. Thus, the present model may be used to explore sex differences in the development of PTSD-like sequelae and to better understand the mechanisms by which PTSD increases risk for cardiovascular disease and myocardial damage following cardiovascular-related incidents.

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Poster

623. Cognition and Anxiety: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 623.15/Y33

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Modeling the effects of paternal lifestyle on the mental health of offspring

Authors: *A. K. SHORT[1], T. Y. PANG[1], A. J. HANNAN[1,2];
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Abstract: The extent of paternal influence was thought to be limited to inherited genetic material. Recent studies have provided evidence that developmental traits may be passed on from the paternal lineage, possibly via non-genetic inheritance through the sperm. To study how paternal stress might influence offspring, a model of chronic heightened hypothalamic pituitary adrenal (HPA) axis activation in male C57Bl/6 mice was used. Mice were supplemented with oral corticosterone (CORT) in drinking water for four weeks before mating with untreated females. Sperm was collected from the epididymis for RNA sequencing. Offspring were then tested for a variety of anxiety and depression-related behaviors starting at PND3 and during young adulthood. Small RNA sequencing revealed that sperm collected from CORT-treated mice had different small RNA distribution profiles. Selective microRNAs predicted to regulate genes involved in anxiety behavior were found to be altered. Male offspring had altered vocalization patterns at PND3 and as adults had increased anxiety-like phenotypes on both the elevated-plus maze and the light-dark apparatus. Changes in expression of anxiety-associated genes in the brains of the male offspring were also observed. This demonstrates that CORT may be instrumental in the transmission of paternal stress induced traits across generations by causing changes in the small RNA populations of sperm. These altered small RNA environments may be having effects in specific offspring tissues, leading to altered phenotypes

Disclosures: **A.K. Short:** None. **T.Y. Pang:** None. **A.J. Hannan:** None.

Poster

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Topic: F.03. Motivation and Emotion

Support: Strategic Research Program for Brain Sciences by the Ministry of Education, Culture, Sports, Science and Technology of Japan

Title: The effect of bimodal value representation on goal directed behavior and reflective choice in behaving macaque

Authors: *M. YASUDA[1], S. NAKAMURA[2], K.-I. OKADA[3], Y. KOBAYASHI[3], K.-I. TSUTSUI[2], K. NAKAMURA[1];
[1]Dept. of physiology, Kansai Med. Univ., Hirakata, Japan; [2]Lab. of Systems Neurosci., Grad. Sch. of Life Sciences, Tohoku Univ., Miyagi, Japan; [3]Labs. for Neurosci. Visual Neurosci. Group, Osaka Univ. Grad. Sch. of Frontier Biosci., Osaka, Japan

Abstract: Gaze is attracted by valuable objects based on past reward learning. During learning, objects may be associated with relative value within local behavioral context, or with absolute value which maintains across contexts. Previous studies investigated behavioral and neuronal correlates of either one of these value representations. However, little is known how those value representations affect our automatic choice of visual object. Here we developed an experimental procedure to test the effect of relative and absolute values on monkey's automatic choice under free viewing. First, the monkey performed a button press task with two fixed sets of 6 visual objects to learn their values. In each trial, one of 6 objects was presented in a pseudorandom order. The monkey was required to react to it by pressing a button, keep pressing for a certain time period, and then release it to obtain a reward. The amount of reward was determined by the object. In the high-valued block (HVb), 3 objects were associated with large (0.11ml); the other 3 with middle reward (0.07ml). In the low-valued block (LVb), 3 were associated with middle (0.07ml); the other 3 with small reward (0.04ml). After performance of this button press task, we tested monkey's gaze in the free-viewing task. In each trial, 4 of trained objects were presented simultaneously, and the monkey was free to look at anywhere. In the button press task, the button-release reaction times (RTs) reflected relative value; shorter in large (middle) reward trials than in middle (small) reward trials in HVb (LVb) (L(mean:562ms) vs. M(653) in HVb, p=5.9x10-16, M(592) vs. S(666) in LVb, p=6.1x10-12, t-test). On the other hand, the button-press RTs represented absolute value across two blocks: shorter in large, intermediate in middle, and longest RTs in small rewarded trials (L(739ms) vs. M(841) in HVb, p =1.5x10-6, M(841) in HVb vs M(859) in LVb, p=0.4, M(859) vs. S(1078) in LVb, p=2.3x10-13). In free viewing, the monkey so far tended to see the objects associated with large reward in HVb more often than the object associated with middle reward in LVb, suggesting the automatic choice represents absolute value of visual objects. The free-viewing tasks which place a few demands on participants would be an ideal tool to investigate cognitive characteristics of psychiatric disorders in humans. Applying this method for the animal may open the way to investigating underlying neural mechanism, and evaluating therapeutic effects of drugs and brain stimulation, such as repetitive transcranial magnetic stimulation and deep brain stimulation.

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Poster

623. Cognition and Anxiety: Animal Models

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Topic: D.04. Vision

Support: Wellcome Trust Grant 095669

Wellcome Trust Grant 095668

Sir Henry Wellcome Trust Postdoctoral Grant

Title: Midbrain dopamine stimulation enhances perceptual sensitivity

Authors: ***A. LAK**[1], S. SCHRÖDER[1], E. JACOBS[1], S. SOARES[2], C. P. BURGESS[1], J. J. PATON[2], K. D. HARRIS[1], M. CARANDINI[1];
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Abstract: Midbrain dopamine (DA) neurons are involved in a variety of cognitive functions such as learning and value-based decision making. In contrast, less is known about how they influence sensory perception and the resulting decisions. We addressed this question by optogenetically stimulating DA neurons in mice, at different stages of a visual decision task. We expressed Channelrhodopsin-2 in midbrain DA neurons via an AAV virus in DAT-Cre mice, and implanted an optical fiber over the ventral tegmental area. Mice were trained to perform a head-fixed visual two alternative forced choice task. In each trial, a grating was presented on the left or right side of monitor, and mice indicated its position by turning a wheel with their forepaws, receiving liquid reward for correct choices. Task difficulty was manipulated by varying stimulus contrast across trials, resulting in high-quality psychometric curves, and reaction times that decreased as a function of stimulus contrast. We first confirmed that DA stimulation at the end of the trial acted as a reward. In alternating blocks of trials, correct choices toward one but not the other response side (left or right) were rewarded not only with liquid but also with phasic optical stimulation of DA neurons. The psychometric curves became markedly biased towards the response side paired with DA stimulation. Moreover, the corresponding reaction times became significantly shorter. These behavioral changes resembled the effects of increasing the amount of

water reward on one side. In animals with unilateral fiber implantation, the behavioral effects were stronger for choices contralateral to the stimulated hemisphere. We then asked how DA stimulation at the time of the visual stimulus would affect perceptual sensitivity. To do so, in randomly chosen trials we phasically stimulated DA neurons prior to or at the onset of the visual cue presentation. Such a manipulation improved performance in difficult trials involving medium to low contrasts, thus resulting in steeper psychometric curves. This improvement in perceptual sensitivity was accompanied by a decrease in reaction time. Together, these results suggest that stimulation of DA neurons during different stages of a perceptual decision task has diverse effects on choice behavior, depending on when such a manipulation is applied. In particular, stimulation of DA neurons during stimulus presentation increased both the speed and the accuracy of detection, effects that resemble those seen with increased attention.

Disclosures: **A. Lak:** None. **S. Schröder:** None. **E. Jacobs:** None. **S. Soares:** None. **C.P. Burgess:** None. **J.J. Paton:** None. **K.D. Harris:** None. **M. Carandini:** None.

Poster

623. Cognition and Anxiety: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 623.18/Y36

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: CIHR MOP-130393

Title: Amelioration of working memory deficits induced by prefrontal cortical GABA hypofunction by D1 receptor stimulation

Authors: ***M. AUGER**[1], N. S. CHAN[1], S. B. FLORESCO[2];
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Abstract: Perturbed prefrontal GABA signalling has been proposed to contribute to cognitive dysfunction associated with schizophrenia. In recent years, work from our group has shown that antagonism of prefrontal GABA-A receptors reproduces many cognitive abnormalities relevant to schizophrenia in rodents, including impairments in working memory as assayed with radial arm maze and delayed non-match to position (DNMTP) tasks. Identifying compounds that can ameliorate these effects may elucidate novel strategies in treating cognitive impairment associated with schizophrenia. D1 receptor agonist drugs have been shown to enhance attention and working memory function at moderate doses. Furthermore, such drugs augment interneuron

excitability and GABAergic inhibition of PFC pyramidal cells, which could potentially reverse the effects of dampened inhibitory neurotransmission. Thus, the goal of this study was to ask whether working memory impairments induced by diminished prefrontal GABA signalling could be rescued by stimulation of dopamine D1 receptors. To this end, male Long Evans rats were trained on an operant version of a DNMTP task. The task consisted of a sample phase in which one lever is extended, and a choice phase in which the subject must select the opposite lever, separated by a variable delay (1-24s). Well-trained animals were implanted with bilateral cannulae in the medial prefrontal cortex (PFC). On test days, animals received counter-balanced infusions of either saline or the GABA-A receptor antagonist, bicuculline (50 ng) and injections of either saline or the D1 agonist SKF 81297 (0.1-0.3 mg/kg, i.p.). Similar to what we have observed previously, antagonism of PFC GABA receptors induced delay-independent impairments in the DNMTP task. However, impairments in working memory performance induced by intra-PFC bicuculline were reversed by concomitant administration of the lower dose of the D1 agonist. Future studies will examine the dose-dependence of these effects and whether D1 agonists rescue impairments induced by prefrontal GABA antagonism in other cognitive tasks. In conclusion, this work suggests that working memory impairments induced by insufficient prefrontal GABA transmission may be reversed by pharmacological stimulation of D1 receptors. As such, pharmaceutical agents that enhance D1 receptor signalling may represent novel treatment strategies for cognitive deficits observed in schizophrenia.

Disclosures: **M. Auger:** None. **N.S. Chan:** None. **S.B. Floresco:** None.

Poster

623. Cognition and Anxiety: Animal Models

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 623.19/Y37

Topic: C.15. Schizophrenia and Bi-polar Disorder

Support: NSERC

Title: The influence of acute stress on individual differences in probabilistic reversal learning

Authors: ***C. A. BRYCE**[1], S. B. FLORESCO[2];
[2]Psychology and Brain Res. Ctr., [1]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: The stress response is a normal physiological reaction that occurs when a threat from the environment causes a disruption in internal homeostasis. Unlike the well-characterized influence of acute stress on learning and memory, the manner in which stress affects more

complex forms of decision-making and cognitive flexibility is poorly understood. Different forms of cognitive flexibility include relatively simple reversal learning, requiring shifts between different stimulus reward contingencies, wherein correct/incorrect responses are always or never reinforced. More complex forms of flexibility are required when "correct" actions are not always reinforced, and may be assessed with probabilistic reversal learning (PRL) assays in both humans and animals. These tests require subjects to keep track of changes in probabilistic reward contingencies, wherein a "correct" choice elicits a reward the majority of the time (80% chance of reward), but an "incorrect" choice also elicits a reward occasionally (20% chance of reward), with these contingencies switching repeatedly over a session. Previous studies have shown that acute stress can either facilitate or impair affects simple reversals, depending on a variety of factors (e.g.; duration, context and timing of the stressor). In comparison, we found that one-hour of restraint stress can differentially affect PRL depending on individual differences in baseline levels of performance. Rats were well trained on a PRL task and then on the test day, were subjected to 1 hr of restraint stress prior to a test session. Rats that displayed "Good" baseline levels of performance (indexed by the number of reversals completed per session) displayed a slight impairment in performance following restraint stress, accompanied by a selective increase in the sensitivity to negative feedback (reward omissions), as indexed by an increase in lose shift behavior. In contrast, in "poor" performers, acute stress reduced negative feedback sensitivity and improved reversal performance. Acute manipulations of serotonin modulates negative feedback, such that decreasing serotonin levels causes an increase in lose-shift behavior in PRL, whereas long-lasting serotonin treatments affect reward sensitivity (Bari et al., 2010). Therefore, ongoing experiments aim to identify the mechanisms underlying the individual differences in PRL following acute stress. These data suggest that acute stress can differentially modulate probabilistic learning, negative feedback sensitivity and cognitive flexibility and may have relevance to understanding abnormalities in these processes that are associated with depression.

Disclosures: **C.A. Bryce:** None. **S.B. Floresco:** None.

Poster

624. Decision Making: Rodents II

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 624.01/Y38

Topic: F.02. Animal Cognition and Behavior

Support: IBS-R001-01

Title: Non-aggressive resolution of conflict between two male mice by resource split behavior

Authors: *I. CHOE, K.-K. KIM, S. PARK, I. KIM, H.-S. SHIN;
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Abstract: The goal of dyadic contest is maximizing the acquisition of the resource while minimizing the cost, such as injury from battle. While it has been theoretically suggested that non-aggressive strategy would be rational when the expected cost exceeds the value of resource, little experimental evidence supports this idea. Therefore, little is known how animals resolve conflict without aggression. Here we show how two freely interacting male mice compete for reward by wireless intracranial electrical stimulation (WICS) on the medial forebrain bundle, a pleasure center. In a test arena equipped with two reward zones, a mouse was able to obtain WICS if it occupied the visually denoted zone first. Contrary to the general expectations in competition, where animals try to monopolize reward, using aggression when necessary, we found that mice resolved conflict non-aggressively using the resource split behavior (RS-behavior), where each mouse obtained reward in different zones and did not intrude the other's zone. The degree of RS-behavior increased over time, and was associated with both the amount of WICS acquired and the equality of acquisition. These suggest that mice learned how to non-aggressively resolve conflict in a mutually benefiting way grounded on economic concerns. This provides insights into when and how non-aggressive resolution can occur during competition.

Disclosures: I. Choe: None. **K. Kim:** None. **S. Park:** None. **I. Kim:** None. **H. Shin:** None.

Poster

624. Decision Making: Rodents II

Location: Hall A

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Program#/Poster#: 624.02/Y39

Topic: F.02. Animal Cognition and Behavior

Support: MH048404

Title: Sex differences measured using a novel paradigm to assess approach and avoidance behaviors

Authors: *T. G. CHOWDHURY[1], N. W. SIMON[1], R. DUTTA[2], J. T. WOOD[1], B. MOGHADDAM[1];
[1]Dept. of Neurosci., Univ. of Pittsburgh, Pittsburgh, PA; [2]Scripps Col., Claremont, CA

Abstract: Men and women have differing incidence rates of various psychiatric illnesses. For example, men are more vulnerable to schizophrenia, autism, and addictions while women are

more susceptible to depression, anxiety, and other mood disorders. The biological basis for these sex differences is unknown. To study sex differences in behaviors that are relevant to psychiatric illnesses, we have developed a novel paradigm for simultaneously testing two different motivated behaviors, namely reward approach and active punishment avoidance, in rats. Rats are first trained on two separate tasks: (1) to perform a nose-poke action to obtain a reward during presentation of a cue, and (2) to perform a lever-press action to avoid an impending foot-shock during a different cue. The identities of the cues and actions were counterbalanced across subjects. After achieving criterion, rats entered the testing phase in which both reward seeking and punishment avoidance behavior were assessed concurrently. On average, male rats obtained a greater proportion of successful responses for reward attainment than females. Females acquired the avoidance behavior faster than males, but upon entering the testing phase, males and females did not differ in the proportion of trials in which they successfully avoided the shock. These results highlight interesting differences between males and females that mirror vulnerability to psychiatric illnesses. Male rats show greater reward-seeking motivation, correlating with the greater incidence of addiction disorders in men. Female rats show more rapid acquisition of avoidance behavior, and this correlates with the greater vulnerability of women to depression and anxiety disorders. These preliminary behavioral data also reveal a great deal of inter-animal variability in both male and female rats. In the future, we are interested in exploring neural and pharmacological correlates of this task, and how these differ as a function of sex.

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Poster

624. Decision Making: Rodents II

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Topic: F.02. Animal Cognition and Behavior

Support: NIH P50 DA05312

NIH R01 DA12964

Title: Effect of social peers on risky decision making in male sprague dawley rats

Authors: *V. WEISS[1], M. T. BARDO[2];
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Abstract: Adolescence is a time associated with increased risk taking, as well as prominent peer relations. Extensive work has shown that adolescents are more vulnerable to peer pressure and advice compared to adults, which leads to exacerbated risk taking. Preclinical research has suggested that these clinical findings may also be applicable to rodents, as adolescent rats find social interaction rewarding and are more prone to risky behavior than adults. There is, however, little research on the effect of social interaction on rodent models of risky decision-making. Recently, an apparatus has been designed by connecting two operant chambers with wire mesh, which allows for two rats to have social contact while performing operant tasks. The current study utilized these social chambers to evaluate the effects of a social peer on behavior in a novel Risky Decision-Making Task (RDMT). In this task, rats were given a choice between a small, safe reward of a single food pellet that is delivered immediately following a response, and a large, risky reward of three food pellets delivered immediately following a response; however, the large reward was also associated with a mild footshock, with the probability of the shock increasing across the session by block (0, 25, 50, 75, & 100%). Adolescent male rats (PND 28 upon start of experiment) were trained in the RDMT either alone (controls) or with their cage mate as a social peer every session until stable responding occurred. Results revealed a main effect of group, such that rats exposed to a social peer were riskier than controls ($p = 0.02$). Rats were then divided into high and low risk-takers within their groups. In controls, high and low risk-takers showed significant differences in risk-taking during all blocks, except for the block associated with 0% chance of shock. In contrast, high and low risk-takers in the social group only showed a significant difference when the chance of shock was 100%. Furthermore, when comparing high and low risk takers across groups (controls vs. social), there were no differences between the high risk-takers, but the low risk-taking rats in the social group were significantly more risky than low risk-taking rats in the control group ($p = 0.01$). These results support clinical work showing that social peers lead to increases in risk taking, and also provide evidence for the ability of social risk-taking to be modeled in rodents. The future goal is to determine the neural systems involved in social facilitation of risky behavior.

Disclosures: **V. Weiss:** None. **M.T. Bardo:** None.

Poster

624. Decision Making: Rodents II

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: F.02. Animal Cognition and Behavior

Support: St Leonard's College Scholarship

Title: Bayesian approach can help analyze and design cognitive flexibility tasks

Authors: J. WANG, *D. S. TAIT, E. M. BOWMAN, V. J. BROWN;
Univ. of St Andrews, St Andrews, United Kingdom

Abstract: Bayesian analysis has recently been used to analyze the data from an intradimensional/extradimensional (ID/ED) attentional set-shifting task in rats, showing that the traditional n-correct-in-a-row learning criterion for the task may cause overtraining or undertraining - and that overtraining may affect rats' performance at the ED shift stage. Here we show two more applications of Bayesian analysis. First, Bayesian analysis can help analyze the detailed learning process in individual rats. In particular, Bayesian analysis of rats' behavior at the ED shift stage of a four consecutive ID task has shown that impaired ED performance in orbital prefrontal cortex-lesioned rats (data from Chase et al., 2012) may result from different causes in different rats, including not only the expected difficulty in shifting attentional set, but also the lack of set-formation in preceding stages, and a lack of attentional focus on either dimension at the ED stage. This suggests that, in future studies of ED shifting ability, researchers may be able to exclude those rats that showed a lack of set-formation or poor attentional focus by investigating individual rat's performance using Bayesian analysis. Second, which bowls contain which perceptual stimuli (e.g., the various odors and media) are traditionally pre-determined pseudo-randomly. Using Bayesian analysis of the previous trials, we can adaptively determine which bowl should contain which stimuli in the current trial by putting the rewarded stimulus into the bowl that the rat is least likely to choose based on preceding choices. Such adaptive design can potentially improve the efficiency of rats' learning by helping rats more quickly focus on the rewarded stimulus. Our investigation suggests that Bayesian analysis, and adaptive-design learning tasks, are powerful tools for data collection and analysis in behavioral studies.

Disclosures: J. Wang: None. **D.S. Tait:** None. **E.M. Bowman:** A. Employment/Salary (full or part-time):; University of St Andrews. **V.J. Brown:** A. Employment/Salary (full or part-time):; University of St Andrews.

Poster

624. Decision Making: Rodents II

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Topic: F.02. Animal Cognition and Behavior

Support: ARC Grant DP130103965

ARC DECRA DE1401000868

Title: Context cues disambiguate the meaning of an extinguished stimulus to guide choice between actions

Authors: *V. LAURENT, B. C. CHIENG, B. W. BALLEINE;
Brain & Mind Res. Inst., Camperdown, Australia

Abstract: Context cues are known to disambiguate the meaning of an extinguished stimulus and control the amount of conditioned responding that such a stimulus can evoke. The present series of experiments examined whether context cues can also control the influence that an extinguished stimulus exerts over choice between actions. We found that a stimulus tested outside of its extinction context acted as a positive predictor of its previously associated outcome, as it biased choice toward an action delivering that same outcome. Extinction cues produced the reversal of this choice. When tested in its extinction context, the stimulus functioned as an inhibitor of its previously outcome, as it biased choice away from an action delivering that same outcome toward an an action earning a different outcome. This reversal of choice was removed by silencing neurons in the infralimbic cortex, consistent with the well-established role of this brain region in the retrieval of extinction. In contrast, silencing of the hippocampus was found to disrupt choice irrespective of the context in which the extinguished stimulus was being tested. Taken together, these experiments indicate that extinction spares the ability of a stimulus to bias choice between actions but the direction of that choice is under the control of the context cues present during extinction training. Interestingly, these extinction cues appeared to imbue the stimulus with net inhibitory properties, which required neuronal activity in the infralimbic cortex to be expressed.

Disclosures: V. Laurent: None. **B.C. Chieng:** None. **B.W. Balleine:** None.

Poster

624. Decision Making: Rodents II

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Topic: F.02. Animal Cognition and Behavior

Support: HHMI

Title: Multi-site optogenetic inactivation of the rat frontal orienting fields and posterior parietal cortex during evidence accumulation

Authors: *C. D. KOPEC[1], J. U. KASDIN[1], C. D. BRODY[2];
[1]Princeton Univ., Princeton, NJ; [2]Princeton Neurosci. Inst., HHMI / Princeton Univ., Princeton, NJ

Abstract: The gradual accumulation of evidence is a fundamental component of decision making, yet the location of the circuit responsible for its implementation remains a mystery. Both optogenetic (Hanks and Kopec et al. Nature 2015) and pharmacological (Erlich et al. eLife 2015) unilateral inactivation of the rat Frontal Orienting Field (FOF, a region of prefrontal cortex) have suggested that while the FOF is required for decisions based on accumulating evidence, it is not part of the accumulation process per se. Instead the data suggested that the FOF is a requisite node that lies downstream of the actual accumulator. Nevertheless, bilateral pharmacological inactivation of the FOF hints at a potential role for it in the accumulation process itself (Erlich et al. eLife 2015). Furthermore, although many neurons in the FOF have firing rates patterns consistent with the FOF being downstream of the graded accumulator, other individual FOF neurons have patterns consistent with encoding graded accumulation itself (Hanks and Kopec et al. Nature 2015). Finally, although bilateral and unilateral pharmacological inactivations of the posterior parietal cortex (PPC) indicated that the PPC plays a minimal role in decisions driven by accumulation of auditory evidence, a behavioral effect of unilateral PPC inactivation could be revealed when combined with simultaneous bilateral FOF inactivation. Here we investigate whether the graded accumulation process is distributed in a redundant fashion across multiple brain areas, with the inhibition of any one region being insufficient to affect the animal's response. The long timescale associated with pharmacological inactivation (~hours) makes it difficult to distinguish effects due to the graded accumulation process from effects due to processes occurring immediately downstream and subsequent to it. We therefore turned to the high temporal resolution afforded by optogenetic inactivation. Using halorhodopsin (eNpHR3.0) in rats performing an auditory accumulation of evidence decision task (the Poisson Clicks Task, Brunton et al. 2013), we probe the effect of simultaneously silencing, only within the graded accumulation period of each trial, either (a) both hemispheres of the FOF; or (b) both FOF and PPC in the same hemisphere. If the circuit responsible for accumulation of evidence is distributed across the two cortical regions probed in each experiment, then simultaneous inactivation of the two should impact the animal's choice, regardless of when during the accumulation period the inactivation occurs.

Disclosures: C.D. Kopec: None. **J.U. Kasdin:** None. **C.D. Brody:** None.

Poster

624. Decision Making: Rodents II

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Support: Human Frontier Science Program (project RG0015/2013),

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Title: Temporal integration in a vibrotactile delayed comparison task: From sensory coding to decision in humans and rats

Authors: A. FASSIHI[1,2], A. AKRAMI[3,4], V. H. SCHÖNFELDER[1], *M. E. DIAMOND[2]; [1]SISSA, Trieste, Italy; [2]Intl. Sch. for Advanced Studies, Trieste, Italy; [3]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [4]Howard Hughes Med. Inst., Princeton, NJ

Abstract: We carried out studies to elucidate how an uncertain tactile stimulus is integrated over time to produce a percept and how that percept is transformed into a decision. Earlier work showed that rats can perform a tactile delayed comparison task with performance overlapping that of human subjects. Subjects discriminate between two vibrations (v1 and v2) delivered either to their whiskers, in rats, or fingertips, in humans. Vibrations are normally distributed velocity noise. The subject must evaluate the two vibrations' relative velocity standard deviations, $\sigma1>\sigma2$ or $\sigma2<\sigma1$. In the present study, vibration duration was varied to investigate how signals are integrated over time. The number of velocity samples grows linearly with vibration duration; the distribution of sampled values approaches the distribution from which they are sampled. Therefore, an ideal observer's estimate of σ will improve with the square root of duration. RESULTS: Both rats and humans showed progressive improvement as vibration duration increased from 100 to 600 ms, provided v1 and v2 were of equal duration. In contrast, unequal duration of v1 and v2 led to a perceptual bias corresponding to an overestimate of σ of the longer stimulus. To account for these observations, we posited that the vibration percept could be approximated by the weighted (exponentially decaying function) sum of speed values over time. Guided by this supposition, we formulated a model that was able to replicate both (i) the subjects' improvement in performance as stimulus duration increased (ii) the bias by which subjects judged longer stimuli as having a greater value of σ. We recorded neuronal activity from rat primary somatosensory (S1) and premotor (PM) cortices. For >30% of S1 neurons, firing rate increased monotonically with σ. PM neurons were heterogenous in their association with various task parameters. About 30% of PM neurons predicted the upcoming decision as the rat integrated v2. Importantly, about 20% of premotor PM neurons encoded v1 during the inter stimulus interval, and their firing was better correlated with weighted sum model than with σ itself. Such neurons appear to encode the animal's percept. These results suggest that a single model,

applicable both to rats and humans, can account for the evolution of the percept of an uncertain stimulus. Moreover the neuronal activity in PM cortex highlights the previously unknown role of this region in stimulus integration and decision making.

Disclosures: **A. Fassihi:** None. **A. Akrami:** None. **V. H. Schönfelder:** None. **M.E. Diamond:** None.

Poster

624. Decision Making: Rodents II

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Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant F32MH098572

Title: Causal contribution and neural encoding of the rat superior colliculus in an accumulation of evidence decision-making task

Authors: ***T. D. HANKS**[1], M. M. YARTSEV[1], C. D. BRODY[2];
[1]Princeton Univ., Princeton, NJ; [2]Princeton University, HHMI, Princeton, NJ

Abstract: Many decision-making behaviors depend on the gradual accumulation of evidence over time. A long line of research has identified neural responses that may be involved in gradual accumulation and subsequent choice categorization over a wide range of brain regions, including multiple cortical areas, the striatum, and the superior colliculus (SC). Here, we used a combination of approaches including electrophysiological recordings, causal perturbations, and computational modeling to examine the role of the rat superior colliculus in an auditory accumulation of evidence decision-making task. We compared these results to those we have obtained previously in other brain regions, such as the frontal orienting fields (FOF) in prefrontal cortex, and the anterior dorsal striatum. Causal perturbations demonstrated that the SC is necessary for decisions driven by accumulation of evidence. Electrophysiological recordings showed that many neurons in the SC exhibit strong pre-movement side-selective responses that gradually develop as the trial unfolds. Furthermore, these firing rate modulations depended on the strength of accumulated evidence, one of the primary identifying characteristics that has been used to suggest a possible role in evidence accumulation. However, when we applied a recently developed computational method to examine the relationship between the firing rates and the value of accumulated evidence (Hanks*, Kopec*, et al. Nature 2015), we instead found that these SC neurons have a more categorical encoding of accumulating evidence. These results suggest

that rather than having a critical role in the graded accumulation process itself, the rat SC may have a more important role in transforming accumulated evidence into a categorical choice, a conclusion similar to one we previously found for the FOF (Hanks*, Kopec*, et al. 2015; Erlich et al. eLife 2015). These results for the FOF and SC stand in contrast to recent findings applying the same toolkit to neurons in the rat anterior dorsal striatum, which were consistent with a role for anterior dorsal striatum in the accumulation process itself (Yartsev*, Hanks*, and Brody Cosyne 2015). Given the direct connectivity of the dorsal striatum through basal ganglia pathways to the superior colliculus, our data suggest a possible route of information flow at the circuit level between neural components that support evidence accumulation and those that support choice categorization based on that accumulated evidence.

Disclosures: T.D. Hanks: None. **M.M. Yartsev:** None. **C.D. Brody:** None.

Poster

624. Decision Making: Rodents II

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Topic: F.02. Animal Cognition and Behavior

Support: HHMI

Title: Time dependent involvement of Posterior Parietal and Prefrontal cortex in a rat auditory parametric working memory task

Authors: *A. AKRAMI[1,2,3], A. EL HADY[1,3], C. D. KOPEC[1,3], C. BRODY[1,2,3];
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[3]Mol. Biol., Princeton Univ., Princeton, NJ

Abstract: Working memory (WM) refers to the ability to store and manipulate information across time intervals of a few seconds. A particular example of working memory task is the sequential comparison of two graded stimuli separated by a delay period of a few seconds, which forces the subject to maintain an analog value in memory. This form of WM is called Parametric Working Memory (PWM) and its neural correlates have been studied in primates (Romo and Salinas 2003). The prefrontal and posterior parietal cortices (mPFC and PPC) have been proposed to be involved in working memory (Pasternak and Greenlee 2005, Harvey et. al 2012, Crowe et al. 2010), but no inactivation experiments probing whether these areas are necessary for parametric working memory have been performed. Moreover, it remains unknown whether the involvement of these brain regions is affected by memory retention time. We have developed

an auditory delayed comparison task in rats, adapted from a tactile task (Fassihi and Akrami et. al 2014). In this task, rats compare two sequential auditory stimuli, 'f1' and 'f2', separated by a variable delay. Stimuli consist of broadband noise (2K-20K Hz), generated as a series of Sound Pressure Level (SPL) values sampled from a zero-mean normal distribution. The rats' task is to decide which of f1 and f2 had greater SPL standard deviation, thus requiring them to hold the analog value of f1 in memory during the delay period. Training steps were formalized into semi-automated computer code, requiring minimal human intervention. Rats show a remarkable ability to hold information about f1 stimulus in their memory for up to 10s (the longest tested). We carry out the first local reversible inactivations of cortical regions to probe their role in PWM, and we show that inactivations of either PPC or mPFC impact this auditory behavior. Interestingly, only PPC inactivation leads to delay-duration dependent impairment. To precisely chart the timecourse of PPC involvement, we optogenetically silenced it, using halorhodopsin (eNpHR3.0), during different time points of the trial. Using a logistic regression model to analyze the specific task components impacted by inactivations, together with electrophysiological recordings, our data suggest distinct roles played by PPC and mPFC in auditory PWM.

Disclosures: **A. Akrami:** None. **A. El Hady:** None. **C.D. Kopec:** None. **C. Brody:** None.

Poster

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McKnight Foundation

Simons Collaboration on the Global Brain

Title: Transient, localized disruption of neural activity in posterior parietal cortex reduces accuracy of visual decisions

Authors: A. M. LICATA, D. N. RAPOSO, *A. K. CHURCHLAND;
Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Integration of uncertain sensory evidence can improve decision accuracy. Pharmacological and chemogenetic inactivations have identified candidate areas that support

evidence integration, including posterior parietal cortex (PPC). However, the slow timescale and large spatial extent of the inactivations mean that PPC has not yet been firmly established as critical for visual decisions requiring evidence integration. Here, we aim to determine the role of PPC in these 'integration decisions' via localized disruption of PPC activity on a fast timescale. We disrupted PPC activity in rats trained to integrate evidence about the rate of visual or auditory events presented over 1000 ms. Rats were injected to express channelrhodopsin-2 (ChR2) pan-neuronally in PPC and were implanted with fibers to allow optical stimulation. Normally, individual PPC neurons are either suppressed or elevated during decision formation, so pan-neuronal stimulation disrupts a dynamic population code. In 2 rats, optical stimulation presented over the 1000 ms decision period reliably reduced accuracy on visual, but not auditory trials. Optical stimulation in an uninjected control rat had no effect. Stimulation could reduce decision accuracy either by weakening the influence of visual evidence on choice or by allowing irrelevant task features to more strongly influence choice. To distinguish these, we fit a logistic regression model to the behavioral data. This revealed that sensitivity to visual evidence was weaker on stimulation trials, while bias and trial history dependence were overall unchanged. Finally, to define the temporal dynamics governing PPC's involvement in integration decisions, we disrupted neural activity during restricted epochs of the decision. Surprisingly, when stimulation took place during the first 250 ms of the decision, accuracy was reduced to the same extent as observed during full 1000 ms stimulation. By contrast, accuracy was largely unaffected when stimulation took place during the last 250 ms of the decision. The effect on accuracy during the middle of the decision (250-500 ms; 500-750 ms) was intermediate. Taken together, our results suggest that PPC activity is required for visual integration decisions, but that the integrated evidence is maintained outside PPC throughout the trial duration. The long-lasting effect of brief stimulation early in the trial suggests that stimulation interrupted an ongoing process that could not recover within the timescale of the trial. This suggests that several hundred milliseconds may be required for the network to re-establish a state that is receptive to visual evidence for decisions.

Disclosures: **A.M. Licata:** None. **D.N. Raposo:** None. **A.K. Churchland:** None.

Poster

624. Decision Making: Rodents II

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 624.11/Z4

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant R01 NS075531

Title: A behavioral task for quantitative assessment of impulsivity in mice

Authors: ***H. PI**[1], T. SIKKENS[3], A. KEPECS[2];
[1]Neurosci., [2]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [3]Univ. of Amsterdam, Amsterdam, Netherlands

Abstract: Impulsivity, a failure of cognitive inhibition in decision-making process, is implicated in diverse psychiatric symptoms including addiction, attention deficit hyperactivity disorders, mania, and borderline personality disorder. The progress has been made in our understanding, yet it remains elusive which neural circuits are involved and how impulsivity is regulated by these circuits. Our long-term goal is to understand neural circuit mechanisms underlying impulsive behavior. As an initial step, we sought a quantitative behavioral assay to assess impulsivity on a trial to trial basis. Therefore we designed a lick withholding task suitable for head-restrained mice. In each trial, in order to receive water reward mice are required to withhold licking until the end of a temporally uncertain delay, signaled by an auditory cue. If the mice lick during the cue presentation, an airpuff is delivered as a punishment. To dissociate impulsivity from temporal and reward expectations we introduce three distinct waiting and reward size contingencies predicted by the auditory cue. The three different trial types are pseudo-randomly interleaved: type 1 - short wait (1.5s) and small reward (3uL); type 2- long wait (3s) and large reward (8uL); type 3 - long wait (3s) and small reward (3uL). Our preliminary behavioral results show that mice could be trained to perform the task reliably. The trained mice (n=2) preferred short wait to long wait (mean performance: type 1 = 0.59+/-0.150; type 2 = 0.47+/-131; type 3 = 0.32+/-0.082; mean +/- standard deviation). Mean reaction times for correct trials were 0.29+/- 0.269 sec (type 1), 0.30+/-0.243 sec (type 2) and 0.79+/-0.627 sec (type 3). Currently, we are designing a computational model for this task to fit the waiting times so that we can extract trial-to-trial impulsivity measures useful for neural studies.

Disclosures: **H. Pi:** None. **T. Sikkens:** None. **A. Kepecs:** None.

Poster

624. Decision Making: Rodents II

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Program#/Poster#: 624.12/Z5

Topic: F.02. Animal Cognition and Behavior

Support: Human Frontier Science Program (project RG0015/2013)

European Research Council Advanced grant, CONCEPT (project 294498)

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European Community's Seventh Framework Programme (project CORONET)

Title: Integration of visual and tactile signals in behaving rats

Authors: *N. NIKBAKHT[1], R. QUIAN QUIROGA[2], D. ZOCCOLAN[1], M. E. DIAMOND[1]; [1]SISSA, Trieste, Italy; [2]Univ. of Leicester, Leicester, United Kingdom

Abstract: Our experience of the world depends on integrating cues from multiple senses to form unified precepts. How the brain merges information across sensory modalities has been the object of debate. To measure how rats bring together information across sensory moralities, we devised an orientation categorization task that combines vision and touch. Rats encounter an object-comprised of alternating black and white raised bars-that looks and feels like a grating and can be explored by vision (V), touch (T), or both (VT). The grating is rotated to assume one orientation on each trial, spanning a range of 180 degrees. Rats learn to lick one spout for orientations of 0±45 degrees ("horizontal") and the opposite spout for orientations of 90±45° ("vertical"). Though training was in VT condition, rats could recognize the object and apply the rules of the task on first exposure to V and T conditions, suggesting that the multimodal precept corresponds to that of the single modalities. Quantifying their performance, we found that rats have good orientation acuity using their whiskers and snout (T condition); however typically performance is superior by vision (V condition). Performance is always highest in the VT condition, indicating multisensory enhancement. Is the enhancement optimal with respect to the best linear combination? To answer this, we computed the performance expected by optimal integration in the framework of Bayesian decision theory and found that most rats combine visual and tactile information better than predicted by the standard ideal-observer model. To confirm these results, we interpreted the data in three additional frameworks: Summation of mutual information for each sensory channel, Generalized linear models, and probabilities of independent events. All three analyses agree that rats combine vision and touch better than could be accounted for by a linear interaction. To study the neuronal correlates of visuo-tactile integration, we are performing electrophysiological recordings in somatosensory, visual and parietal association areas.

Disclosures: N. Nikbakht: None. **R. Quian Quiroga:** None. **D. Zoccolan:** None. **M.E. Diamond:** None.

Poster

625. Executive Function: Models of Disorders

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 625.01/Z6

Topic: F.02. Animal Cognition and Behavior

Title: Anxiolytic-like effects of n-sustituted melatonin analogues on mice

Authors: *A. ALMARAZ, E. B. NARANJO-RODRIGUEZ, A. S. LIRA-ROCHA, A. M. VÁZQUEZ;
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Abstract: Melatonin (MT) is a Pineal hormone that regulates several physiological processes, circadian rhythms, reproductive and modulates neuroendocrine function. And anticonvulsivant, sedative, hypnotic, anxiolytic and antidepressive-like pharmacological effects. On the other hand, Diazepam (DIAZ) has been used for long time as a treatment, however; produces several adverse effects. For this reason this research is aimed to find alternative therapies at anxiety treatment with modified molecules at functional groups, such as MT Analogues. This study was carried out in CD1 male mice (22±3g) with Marble-Burying Test as a model of anxiety and, ED50 were calculated by statistical analysis. All the mice were administrated with DIAZ (0.25,0.5 mg/kg), MT (0.5,1.0,2.0 mg/kg) and 1-N substituted Analogues [(M6A and M7A) (0.125,0.25,0.5,1.0,2.0 mg/kg)] . The results obtained showed that MT Analogues had more effectiveness as anxiolytic-like that MT and DIAZ. This project was supported by DGAPA-PAPIIT-UNAM. Key IT201112-2

Disclosures: A. Almaraz: None. **E.B. Naranjo-Rodriguez:** None. **A.S. Lira-Rocha:** None. **A.M. Vázquez:** None.

Poster

625. Executive Function: Models of Disorders

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Program#/Poster#: 625.02/Z7

Topic: F.02. Animal Cognition and Behavior

Support: Agentschap NL BSIK03053

Title: Rapid and refined screening of behavioral flexibility, impulsivity and attention in mice using different types of automated home-cage tasks

Authors: *E. REMMELINK[1,2,3], M. VERHAGE[3], A. B. SMIT[2], M. LOOS[1];
[1]Sylics, Amsterdam, Netherlands; [2]Mol. and Cell. Neurobiology, CNCR, [3]Functional Genomics, CNCR, VU Univ., Amsterdam, Netherlands

Abstract: Several brain disorders, such as schizophrenia, autism and Alzheimer's disease, are characterized by deficits in cognitive flexibility, attention and inhibitory control. The majority of currently available behavioral tests to assess these executive functions in animal models of brain disorders are labor intensive, require imposed food-restriction regimes and involve extended training periods. Therefore, we investigated whether in a home-cage setting, with 24-hour access to an operant task and without imposed food-restriction regimes, mice would reach similar performance levels in a shorter training period. We describe 3 new operant protocols for automated home-cages that measure behavioral flexibility, sustained attention, impulsivity, and attentional set-shifting. 1. First, we developed a reversal learning task that effectively measures initial discrimination learning and behavioral flexibility within 4 days in an automated home-cage. C57BL/6J mice were able to attain the performance criterion of 80% correct within 1 day. Reversal learning requires suppression of the initially acquired response, while learning a new, competing rule. As expected, mice took significantly longer to attain the performance criterion during the reversal phase, confirming the idea that we tested behavioral flexibility. In line with previous studies, lesions of the orbitofrontal cortex led to a specific reversal learning deficit. 2. We adapted a five choice serial reaction time task (5CSRTT) for mice towards a home-cage setup. Typically, 10 - 14 weeks of daily training sessions are required to measure performance in a conventional setup. Automation significantly reduced total training time to 2 weeks with levels of accuracy, omissions, and premature responses comparable to those obtained in the conventional setup. 3. We designed a novel attentional set-shifting protocol for an operant home-cage setup, in which mice successfully completed 2 reversals and 1 dimensional shift within 2 weeks. We observed impairments in mouse lines with well-known deficits in executive function (e.g. APP/PS1, Fmr1 and some BXD strains) in these automated tasks, replicating as well as extending previous results. In all tasks, activity was predominantly limited to the dark phase, suggesting that 24-hour access to the task had no impact on circadian rhythm. In conclusion, we show that various tasks measuring executive functions can be implemented effectively in automated home-cage setups without imposed food-restriction regimes, providing an efficient, robust and improved way of testing mice for executive abilities.

Disclosures: E. Remmelink: None. **M. Verhage:** None. **A.B. Smit:** None. **M. Loos:** None.

Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Support: Polish-Swiss Research Programme grant - PSPB-210

Title: Eco-HAB - fully automated and ecologically relevant assay for individualized measurement of social impairments in mouse models of autism

Authors: *A. PUSCIAN[1], S. ŁęSKI[1], M. WINIARSKI[1], P. BOGUSZEWSKI[1], G. KASPROWICZ[2,3], E. KNAPSKA[1];
[1]Nencki Inst. of Exptl. Biology, PAS, Warsaw, Poland; [2]Ctr. for Theoretical Physics, Polish Acad. of Sci., Warsaw, Poland; [3]Inst. of Electronic Systems, Warsaw Univ. of Technol., Warsaw, Poland

Abstract: Impairments of social interactions are a key feature of autism spectrum disorders. Although there exist behavioral assays designed for evaluation of conspecific-related behavior in mice, available tasks do not allow for longitudinal observations of spontaneous interactions between littermates. Furthermore, the experiments are usually carried out on isolated animals and require their handling by an experimenter. These factors may exert confounding, anxiety-related effects on obtained data and result in large between-laboratory variability. In order to alleviate these problems, we designed Eco-HAB - a fully automated, stress-reducing tool for an individualized assessment of voluntary social interactions in group-housed mice. Using Eco-HAB, we assessed social approach of male and female Fmr1 knock-out mice of the FVB strain. Expansion of the CGG trinucleotide repeat affecting the Fragile X mental retardation 1 gene is the most widespread single-gene cause of autism. We determined that in accordance with previously documented deficits, Fmr1 knock-out male subjects show less social approach behaviors than respective controls. On the contrary, Fmr1 knock-out females display an enhanced pattern of exploration oriented towards olfactory stimuli of the conspecific-provenience. Besides sex differences, we were also able to assess individual level of social approach behavior for each investigated subject, due to an RFID-based animal tagging. We argue that when utilizing mouse models of autism for developing therapeutic strategies, one should focus on particular behavioral impairments, corresponding to individual symptoms in patients, rather than try to address a rarely appearing all-inclusive phenotype. Eco-HAB enables such research, asserts high reliability and reproducibility. It imitates natural habitat by taking into account specific features of murine behavior. Therefore, we claim that Eco-HAB is a valuable and reliable tool for the assessment of social interactions and gathering knowledge of social relations in-group housed mice.

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Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Support: NIEHS R01 ES015295

Title: Low level lead exposure differentially impairs cognitive flexibility in an attentional set shifting task dependent upon sex and developmental period of exposure

Authors: *L. S. NEUWIRTH, D. W. ANDERSON, J. S. SCHNEIDER;
Pathology, Anat. and Cell Biol. Med., Thomas Jefferson Univ., Philadelphia, PA

Abstract: Low level lead (Pb) exposure impairs a variety of cognitive processes. Children exposed to Pb developmentally present with cognitive impairments that include deficits in learning, memory, language and executive functioning, yet experimental work on Pb toxicity in rats has focused mostly on hippocampal dependent learning and memory deficits and less on executive functions. However, detrimental effects on executive functioning could result in or even underlie a variety of other cognitive problems attributed to Pb exposure. We examined the ability of Long Evans male and female rats (control and Pb-exposed: 150ppm Pb-acetate in food given perinatally (Peri, gestation through weaning) or early postnatally (EPN, birth through weaning) to acquire and perform an attentional set shifting test (ASST) that requires locating a food reward by discriminating between digging materials and odors. The tasks consisted of simple (SD) and compound (CD) discriminations and reversals, intra-dimensional (ID) and extra-dimensional (ED) shifts followed by reversals (Rev). The performance of control females differed from males only at the ID-Rev stage. Pb-exposed male and female rats exhibited sexually distinct cognitive impairments depending on the developmental time period of Pb exposure. EPN Pb-exposed male rats were unable to perform the SD with odors and were incapable of performing the CD tasks to complete the ASST. In contrast, Perinatal Pb-exposed males were able to complete the entire ASST, but had deficits in the ID and ID-Rev stages compared to controls. EPN Pb-exposed females, unlike EPN Pb-exposed males, were able to complete the ASST and had impairments in the ED and ED-Rev stages. Perinatal Pb-exposed females also were able to complete the ASST and had deficits in the ED and ED-Rev stages. These data suggest that fronto-executive functions may be regulated in a sex dependent manner. Moreover, low level Pb exposure results in executive dysfunction dependent upon sex and the developmental exposure period. In particular, Pb may impair the ability to form, maintain and shift response sets contributing to deficits in cognitive flexibility.

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Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant AA019462

Title: Moderate prenatal alcohol exposure alters hippocampal functional network connectivity and social behavior in adult long evans rats

Authors: ***C. I. RODRIGUEZ**[1], S. DAVIES[2], V. CALHOUN[3,4], D. SAVAGE[2], D. HAMILTON[1];
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Abstract: It is well established that heavy ethanol exposure during prenatal brain development leads to profound cognitive and behavioral consequences. In contrast, the effects of moderate prenatal alcohol exposure (MPAE) are less severe yet persistent. Prior research has showed alterations of hippocampal functioning as a result of MPAE. Additionally, the hippocampal complex has been implicated in a number of social behaviors. Here we investigate whether MPAE alters functional network connectivity (FNC) in the hippocampus and its association to social behavior. To accomplish this, we applied independent component analysis (GICA) to functional MRI data gathered from Long-Evans rats exposed to 5% ethanol or saccharin throughout gestation. In adulthood, rats were anesthetized (1.0-2.3% isoflurane) and BOLD signals were acquired during a 10 min echoplanar imaging sequence in a 4.7T Bruker Biospin scanner. Following motion correction, spatial normalization and smoothing, spatial independent component analysis (ICA) was performed using the Infomax algorithm implemented in the GIFT toolbox (http://mialab.mrn.org/software/gift). A total of 17 non-artifactual components were retained for analysis of connectivity measured through component cross-correlations. Components were observed in cortical, hippocampal, striatal, thalamic, and cerebellar structures. We focused our analyses on the correlations between the frequency of wrestling behavior and FNC between components localized in the hippocampus and other brain regions. Saccharin controls and ethanol-exposed animals showed more negative correlations between measures of wrestling and hippocampal FNC. When compared to saccharin animals, ethanol animals also displayed a slight increase in the number of positive associations between FNC and behavior.

When examining males, more negative rather than positive correlations between FNC and behavior were observed. Ethanol-exposed males also displayed a decrease of negative associations between FNC and behavior. Saccharin and ethanol-exposed females displayed more positive, associations between FNC and behavior. In contrast to males, however, female animals displayed more positive associations between FNC and behavior for both treatment conditions. These results indicate that moderate fetal ethanol exposure can have long-lasting consequences on hippocampal functional connectivity, and these alterations are predictive of alterations in social behavior.

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Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant MH086530

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University of Michigan funds

Title: Elevated brain cytokine levels associated with cognitive vulnerability of CHT+/- mice following repeated mild traumatic brain injury

Authors: *A. KOSHY CHERIAN[1], N. C. TRONSON[1], V. PARIKH[2], R. D. BLAKELY[3], M. SARTER[1];
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Abstract: Repetitive mild traumatic brain injury (rm-TBI), as sustained by athletes and military personnel, is one of the most common types of brain injury resulting in persistent, particularly attentional, impairments. Loss of or attenuated cholinergic functioning has long been hypothesized to greatly contribute to rm-TBI-induced cognitive symptoms. Because choline transporter (CHT) heterozygosity limits the capacity of cholinergic neurons to sustain elevated levels of cholinergic activity, we hypothesized that rm-TBI yields more severe attentional-

cholinergic consequences in CHT+/- mice. CHT+/+ and CHT+/- mice acquired the mouse version of the Sustained Attention Task (SAT; St.Peters et al., 2011) and then were subjected to rm-TBI using a modification of the method described by Kane et al. (2012). Mice practiced the SAT 5 - 6 days a week and received five TBI events distributed over 35 days. Rm-TBI did not impair the performance of WT mice but, beginning after the 3rd impact and persisting thereafter, greatly impaired the detection rates of CHT+/- mice. In a separate group of mice, 7 days/SAT sessions after the final impact we harvested frontal cortical tissues for saturation analyses of hemicholinium-sensitive choline uptake in synaptosomes. Choline uptake (Vmax) was mildly but significantly reduced in WT mice subjected to rm-TBI. Rm-TBI nearly completely abolished choline uptake in CHT+/- mice. However, this effect was not associated with a loss of total CHTs, cholinergic terminals or synaptic contacts in general, suggesting a regulatory silencing of CHTs following rm-TBI in CHT+/- mice. To determine a potential mediator of this effect of rmTBI, and guided by hypotheses linking cholinergic activity with inflammatory mechanisms, we determined brain cytokine/chemokine levels in tissues harvested 7 days after the final impact. Compared with CHT+/+ mice subjected to rm-TBI, levels of IL-2, CCL3, CCL4, IL-9, and IL-13 were significantly elevated in CHT+/- mice. These results suggest that elevated cytokine levels may interfere with normal CHT function and therefore mediate the attentional-cholinergic vulnerabilities of subjects expressing subcapacity variants of cholinergic neurons or with declining cholinergic systems.

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Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Support: IU Collaborative Research Grant 2214044

Title: Persistent alterations in cortical structure and function following maternal deprivation in the rat

Authors: *S. S. JANETSIAN[1], M. M. TIMM[1], A. M. MCCANE[1], A. J. BAUCUM, II[2,3], B. F. O'DONNELL[4], C. C. LAPISH[1,3,5];
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Med. Stark Neurosci. Res. Inst., Indianapolis, IN; [4]Dept. of Psychological and Brain Sci., Indiana Univ., Bloomington, IN; [5]Sch. of Sci. Inst. for Mathematical Modeling and Computat. Sci., Indiana University-Purdue Univ. Indianapolis, Indianapolis, IN

Abstract: Early life traumatic experiences or exposure to stressful environments may predispose an individual to develop a neuropsychiatric disorder or health problems later in life, including schizophrenia (SZ) or depression. Animal models have played a critical role in understanding how adverse events early in life may evoke changes in biomarkers of altered brain function and altered behavioral phenotypes that resemble these neuropsychiatric disorders. However, SZ is a complex condition with a multifactorial etiology, which makes it difficult to model the breadth of this condition in a single animal model. Considering this, it is necessary to develop rodent models that model clearly defined subsets of pathologies observed in the human condition and their developmental trajectory. One of the most widely used animal models to induce SZ-like symptoms is the maternal deprivation (MD) model. This models an early life traumatic event via exposure to a stressful event in the postnatal period. The current study assessed how an early life traumatic event alters cognition and brain function to better understand what neural systems might be compromised following these events. On postnatal day (PD) 9, male rat pups were maternally deprived (MD) for 24-hours or were left undisturbed. In Experiment 1, recognition memory was tested in adulthood using the novel object recognition task. Then, tissue was extracted and expression of catechol-o-methyl transferase (COMT) and glutamic acid decarboxylase (GAD67) were quantified in the prefrontal cortex (PFC), striatum, and temporal cortex (TC). In Experiment 2, electrophysiological recordings were obtained from the PFC, vertex, and TC during a paired-click paradigm to assess the effects of MD on sensory gating. Locomotor activity, root mean squared (RMS) voltage signal, and a gating ratio were quantified between groups. Impaired recognition memory was observed in MD animals. Compared to shams, MD animals had lower expression of COMT in the PFC and TC, and lower expression of GAD67 in the TC only. No differences were observed in the striatum. In Experiment 2, MD animals had an increased RMS voltage in all three recording sites and increased locomotor activity compared to shams. Lastly, MD animals had a blunted gating response during the paired-click paradigm compared to shams, which was most pronounced in the TC. These data suggest that neurodevelopmental perturbation early in life was associated with long-lasting alterations in cognition and brain function in adulthood. As such, this model may provide a useful tool to further explore the neural basis of early life trauma that may result in mental psychiatric disorders, including SZ.

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Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Support: CONACYT 167016

PAPIIT IN306415

Title: Sensitivity to delay of reinforcement, but not sensitivity to amount, correlates with impulsivity in Spontaneously Hypertensive Rats

Authors: *V. ORDUÑA, O. ZAMORA;
UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO, MEXICO, Mexico

Abstract: In previous reports, we have shown that Spontaneously Hypertensive Rats (SHR), an animal model of Attention Deficit Hyperactivity Disorder (ADHD) show higher levels of impulsive behavior in a free operant choice task, are more sensitive to the delay of reinforcement, and are equally sensitive to the amount of reinforcement than Wistar (WIS) rats. These results were obtained from experiments using separate groups of experimental subjects. In the present report, 9 SHR and 9 WIS rats participated in three tasks: one of them measured impulsivity, while the other two were short versions of the tasks measuring sensitivity to amount and sensitivity to delay. The results replicated the results reported before: SHR were more impulsive and more sensitive to delay, but equally sensitive to amount. In addition, we found a positive correlation between the degree of impulsivity and the degree of sensitivity to delay; impulsivity and sensitivity to amount were found to be no correlated.

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Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Support: KAKENHI26460073

Title: The significance of highly basic C-terminal region of Reelin for behavior

Authors: K. SAKAI[1], H. SHOJI[2], T. KOHNO[1], T. MIYAKAWA[2,3], *M. HATTORI[1];
[1]Nagoya City Univ., Nagoya, Japan; [2]Fujita Hlth. Univ., Toyoake, Japan; [3]Natl. Inst. Physiol. Sci., Okazaki, Japan

Abstract: Reelin is a large secreted glycoprotein that is required for normal brain formation. In adult brain, Reelin malfunctions have been suggested to play critical roles in the pathogenesis of neuropsychiatric disorders, including schizophrenia, bipolar disorder, and autism. Reelin protein is composed of N-terminal domain, Reelin repeats, and highly basic C-terminal region (CTR). The primary sequence of the CTR is conserved in most vertebrates, suggesting its importance. We generated knock-in mice lacking Reelin CTR (ΔC-KI mice, Kohno et al., J. Neuosci. 35, 4776 (2015)). In the ΔC-KI mice, layer structures of the cerebral cortex and the hippocampus are partially abnormal. To reveal functions of the CTR in adult brain, we analyzed behavior of the ΔC-KI mice by comprehensive behavioral test battery. Between the ΔC-KI and wild-type mice, there was no difference in sociability, spatial memory, depression-like behavior, prepulse inhibition of acoustic startle response, and cued and contextual fear memory. ΔC-KI mice fell from a wire lid earlier than wild-type mice in wire hang test, while they remained longer on a wheel in rotarod test. We assume that results of wire hang and rotarod tests derive from hyperactivity of ΔC-KI mice (see below). The ΔC-KI mice were hyperactive and exhibited reduced anxiety-like behavior in open field test and elevated plus maze test, respectively. There was no difference in reference memory between the ΔC-KI and wild-type mice, while working memory of the ΔC-KI mice was impaired compared with the wild-type mice in T-maze test. These observations suggest that the CTR of Reelin is required for normal locomotor activity and working memory function. Thus, the ΔC-KI mice may be useful as a model of psychiatric disorders characterized by hyperactivity and working memory deficits, such as autism and attention deficit hyperactivity disorder.

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Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Support: BGRO, Georgetown University

Title: Situational and age-dependent decision making during life threatening distress in myotis macrodactylus

Authors: X. HUANG[1], T. JIANG[1], Z. LONG[1], B. LUO[1], X. YUE[1], Y. GU[1], J. FENG[1], *J. S. KANWAL[2];
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Abstract: Echolocation and audiovocal communication have been studied extensively in bats. The manner in which these abilities are incorporated within escape behaviors during life-threatening distress is largely unknown. Here we tested whether behavioral response profiles expressed during distress are relatively stereotypic or vary with the individual, the context and the animal's age. We subjected juvenile and adult big-footed Myotis (Myotis macrodactylus) to a sequence of three types of life threatening distress: 1) trapping them in a mist-net (environmental threat), 2) approaching them when trapped (predator threat), and 3) partially restraining their freedom to move (arrest), and made audio-video recordings of their escape behaviors in each condition. Response profiles differed across individuals and with the context in which they were expressed. During environmental and predator threat, bats displayed significantly more biting and wing-flapping behaviors and emitted more echolocation pulses than during arrest. Response profiles also varied with age. During arrest, juveniles were more likely than adults to emit distress calls and vice-versa for biting and wing flapping during environmental and predator threat. Overall, individualized response profiles were classified into ten clusters that were aligned along two divergent response trajectories when viewed within two-dimensional, multifactorial decision space. Juvenile behaviors tended to follow a predominantly “social-dependence” trajectory, whereas adult behaviors were mostly aligned along a “self-reliance” trajectory. We conclude that bats modify their vocal behavior and make age-appropriate and contextually adaptive decisions when distressed. This decision-making ability is consistent with observations in other social species, including humans.

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Poster

625. Executive Function: Models of Disorders

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 625.11/Z16

Topic: F.02. Animal Cognition and Behavior

Support: Japan Society for the Promotion of Science(JSPS) KAKENHI Grant Number 26460338

JSPS Research Fellow 26・5605

Title: EP4 receptor-associated protein (EPRAP) deficient mice exhibited behavioral abnormalities

Authors: *R. FUJIKAWA, M. MINAMI, S. HIGUCHI, M. YASUI, T. IKEDO, M. NAGATA, M. YOKODE;
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Abstract: Background and aims: EP4 receptor-associated protein (EPRAP) is a newly identified molecule regulating macrophage activation. Recently we have demonstrated that EPRAP exists abundantly in the brain; however, little is known about the function of EPRAP in the brain. EPRAP specifically localized in glial cells: therefore, we hypothesized that EPRAP may be involved in emotion or behavior. Methods: Behavioral tests were performed with 5-month-old, male EPRAP deficient mice (KO) and wild-type C57BL/6 mice (WT) (n=16, each). First, we examined general health and neurological screening including wire hang test. Motor coordination and balance were tested with rotarod test. Locomotor activity and anxiety-like behavior were measured using open field test, plus maze test and light/dark transition test. Porsolt forced swim test was performed to evaluate despair-like behavior. Working memory performance was tested with radial maze. Social behavior was assessed by Crewley's social interaction test. Startle response was tested in pre-pulse inhibition test. Finally, EPRAP-KO and WT mice were injected intraperitoneally with methylphenidate (MPH), a dopamine reuptake inhibitor, at a dose of 30mg/kg. The effect of MPH on locomoter activity was examined by open field test. Results: EPRAP-KO mice didn't show abnormality in general health. In wire hang test, latency to fall was significantly decreased in EPRAP-KO mice compared to WT mice. There were no significant differences in despair-like behavior and working memory and motor coordination between WT mice and EPRAP-KO mice. However, compared to WT mice, EPRAP-KO mice showed increased locomoter activity in some tests. Furthermore, EPRAP-KO mice decreased anxiety-like behavior and startle response. Social novelty preference is increased in EPRAP-KO mice. After MPH administration, locomoter activity in EPRAP-KO mice was less increased compared to WT mice. Conclusion: EPRAP-KO mice exhibited behavioral abnormalities including locomotor activity, abnormal anxiety-like behavior, and startle response, which partially recapitulate the symptoms of attention deficit hyperactivity disorder (ADHD) or schizophrenia. Additionally, we demonstrated that EPRAP-KO mice decreased the response to MPH. Because dopamine signaling is closely related to the symptoms of ADHD or schizophrenia, dysfunction of dopamine could be a cause of these behavioral abnormalities in EPRAP-KO mice. EPRAP may participate in the pathogenesis of behavioral disorders and could be a novel therapeutic target for mental diseases.

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Poster

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Topic: F.02. Animal Cognition and Behavior

Support: NIH-R15MH093918-01 A1

Title: Behavioral and biochemical consequences of simulated vehicle exhaust exposure

Authors: ***A. A. SALVI**[1], G. PATKI[2], H. LIU[2], S. SALIM[2];
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Abstract: Air pollution from vehicle exhaust leads to 800,000 premature deaths annually. While most attention is focused on air pollution-related pulmonary and cardiovascular complications, its impact on mental health is often ignored. Carbon dioxide (CO2), carbon monoxide (CO) and nitrogen dioxide (NO2) present in exhaust are pro-oxidants. Our laboratory has established that increased oxidative stress in the brain leads to behavioral deficits such as anxiety-, depression-like behaviors and cognitive impairment in rats. Thus prolonged exposure to pro-oxidants present in vehicle emissions also might increase levels of oxidative stress ultimately leading to behavioral deficits. Here, we simulated vehicle exhaust exposure in a laboratory setting and observed that sub-chronic exposure to this simulated system induced behavioral deficits in rats. Adult male Sprague Dawley rats were exposed to a mixture of 1.3% CO2, 100 ppm NO2 and 0.06% CO with air as a base in regulated whole body exposure chambers. This mixture resembles the composition of pro-oxidants in vehicle exhaust diluted in a ratio of 1:10 with air. The exposure was performed for 30 min daily for a period of 2 weeks. A separate control group of rats was exposed to normal air for the same duration. Following exposure, behavioral analysis was performed to assess anxiety-like behavior (open-field, elevated plus maze and light-dark tests), depression-like behavior (forced swim test) and cognitive impairment (Morris water maze test). This was followed by biochemical analysis to measure the increase in oxidative stress (Enzyme Immunoassay based tests) following exposures. We observed increased anxiety-like and depression-like behavior as well as impaired short-term and long-term memory in rats exposed to simulated exhaust. Biochemical analysis showed elevated levels of corticosterone (systemic stress marker) and 8-isoprostane (oxidative stress marker) in the plasma of exposed rats indicating an increase in oxidative stress following exposure to simulated exhaust. In

conclusion our study identifies sub-chronic simulated vehicle exhaust exposure-induced behavioral and biochemical deficits. This study is expected to reveal the negative impact of vehicle exhaust exposure on the brain and its repercussions on mental health.

Disclosures: **A.A. Salvi:** None. **G. Patki:** None. **H. Liu:** None. **S. Salim:** None.

Poster

625. Executive Function: Models of Disorders

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Program#/Poster#: 625.13/Z18

Topic: F.02. Animal Cognition and Behavior

Title: Touchscreen tasks for cognitive phenotyping of rats exposed to a chronic mild stress model of depression

Authors: ***L.-S. MARTIS**[1], S. KROG[1], C. BRISION[1], A. MØLLER[2], O. WIBORG[1]; [1]Translational Neuropsychiatry Unit, Aarhus Univ., Risskov, Denmark; [2]Dept. of Clin. Med., Ctr. of Functionally Integrative Neurosci., Aarhus University, Denmark

Abstract: Background: Major depressive disorder (MDD) affects 350 million people worldwide designating it as the second leading cause for disability. Patients suffering from depression show cognitive impairment and anhedonia, one of the core symptoms indicating diminished anticipation and feelings of pleasure. To further develop, optimize and verify antidepressant treatment and therapeutic strategies, valid animal models are essential. Since stress is the main environmental risk factor for developing depression, we aim to model MDD by applying the chronic mild stress (CMS) paradigm, in which rats are exposed to a series of unpredictable stressors over weeks. Following stress exposure, rats are defined as stress-susceptible or resilient based on their consumption of a palatable sucrose solution, which is used as a measure of their reward sensitivity. Methods: We apply the Bussey-Saskida touchscreen (TS) operant platform in combination with the CMS paradigm to evaluate possible alterations in cognitive functions, specifically regarding memory consolidation, perseveration, stimulus-reward association and paired-association learning. Advantages of the TS technique include automation, diminution of experimenter's bias, objective and standardized readouts, good translatability to the human CANTAB (Cambridge Neuropsychological Test Automated Battery) test, countless modifications of the visual stimuli and a test battery for more precise cognitive phenotyping. Results and Perspectives: Preliminary results show that memory retrieval is impaired in the CMS group after a period without TS training, whereas non-stressed controls keep a consistent performance. Stress exposure alone does not seem to have an effect on simple executive

functions like stimulus-reward association learning. Therefore, we are currently investigating the CMS subgroups of anhedonic-like and resilient animals separately to accentuate potential phenotypic differences. Furthermore, advanced and more cognitive demanding TS tasks are applied to detect even subtle cognitive alterations in dependence of the rats' phenotype.

Disclosures: L. Martis: None. **S. Krog:** None. **C. Brision:** None. **A. Møller:** None. **O. Wiborg:** None.

Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Title: Bone marrow-derived mesenchymal stem cells improve diabetes-induced cognitive impairment by secreting exosomes and repair neurons and astrocytes

Authors: *M. NAKANO, K. NAGAISHI, N. KONARI, T. CHIKENJI, Y. MIZUE, M. FUJIMIYA;
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Abstract: BACKGROUND: Diabetes is a risk factor for cognitive decline. It is known that diabetes impairs neurons and astrocytes in hippocampus leading to learning and memory disturbance. Recently we found that intravenous injection of bone marrow-derived mesenchymal stem cells (MSCs) ameliorate diabetes-induced cognitive impairment and these cells are potent to repair damaged neurons and astrocytes. In this study, we aim to investigate why intravenously injected MSCs can reverse the damaged cells by focusing the exosomes secretion from injected MSCs. METHODS: Diabetes mouse model was produced by an intraperitoneal (ip) injection of streptozotocin (STZ, 150 mg/kg). MSCs were isolated from bone marrow of rats and administered via the tail vein at 12, 14, 16, 18 weeks after STZ injection. After 20 weeks of STZ injection, learning and memory behavior was measured using Morris Water Maze (MWM) test and mice were sacrificed for morphological study. We also injected PKH-labeled MSCs intravenously to evaluate distribution of MSCs in the brain. On the other hand, exosomes (0.5 μg of protein) were isolated from the culture media of MSCs and injected intracerebroventricularly (icv) for 5 successive days at 12 weeks after STZ injection. Two days after last icv injection, MWM test was conducted and mice were sacrificed for analyses. We also injected PKH-labeled exosomes icv to evaluate their distribution in the brain. RESULTS: The MWM test demonstrated that cognitive impairment induced by diabetes was completely recovered by both MSCs and

exosomal treatment. In the CA1 region of the hippocampus, degeneration of neurons and astrocytes as well as synaptic loss were prominent in diabetes, however MSCs and exosomal injection successfully normalized them. After injection of PKH-labeled MSCs, very few MSCs were detected in the brain parenchyma although amounts of labeled MSCs were detected in the lung or other organs. On the other hand, a large number of injected PKH-labeled exosomes were found in the brain parenchyma and they were internalized into astrocytes and neurons. CONCLUSIONS: The results suggest that exosomes derived from MSCs may contribute to repair the damaged neurons and astrocytes in diabetes and subsequently recover the cognitive impairment. This study provides a new therapeutic strategy for diabetes-induced cognitive impairment.

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Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Support: NIH 1R01 NS063009

Title: Cerebellar neuropathology influences cerebellar-nucleus accumbens, striatum, and prefrontal cortex pathways in modulating dopamine release in the Fmr1 strain: Relevance to Autism Spectrum-related behavioral disorders

Authors: *E. MCKIMM[1], D. M. COOMES[1], Z. R. HOLLOWAY[1], M. CALTON[1], D. GOLDOWITZ[2], G. MITTLEMAN[1], C. D. BLAHA[1];
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Abstract: Autism spectrum disorders are neurodevelopmental disorders that traditionally encompass autism, Asperger's syndrome and pervasive developmental disorders not otherwise specified (APA, 2013). Autism is characterized by at least two neural abnormalities: cerebellar pathology including Purkinje cell loss or dysfunction as well as dopaminergic (DA) and glutamatergic changes among multiple cerebellar-prefrontal cortex (PFC) pathways. Electrical stimulation of the deep cerebellar dentate nucleus (DN) is attenuated in Lurcher (Lc) mutant mice lacking Purkinje cells (Mittleman et al. 2008). Fmr1 knockouts (mutants) are a commonly used model of Fragile X syndrome and exhibit cerebellar abnormalities such as elongated

Purkinje cell spines and decreased cerebellar nuclei volume (Ellegood et al., 2010; Koekkoek et al., 2005; Goodrich-Hunsaker et al., 2011; Verkerk et al., 1991). Rogers and colleagues (2011) have shown PFC DA transmission elicited by electrical stimulation of the DN in Fmr1 knockouts produces similar results to the Purkinje cell absent Lc mutants. The Fmr1 strain also has projections from the DN to the striatum and the nucleus accumbens (NAc), as well as DA transmission in both of these pathways (McKimm et al., 2014). Individuals with Autism often exhibit cognitive and behavioral deficits with regards to movements, executive functions, and reward learning, such as habitual actions and preoccupation of specific obsessions. In the present study we explore the potential influence of dysfunctional Purkinje cells within the Fmr1 strain on the behavioral and cognitive abnormalities of the striatum and NAc, specifically in the dorsomedial (DMS) and dorsolateral striatum (DLS) as well as the NAc core (NAcc) and NAc shell (NAcsh). The striatum is associated with learning and performance associated movement as well as some executive functions. The NAc is associated with motivation, pleasure, and reward-reinforcement based learning. Fixed potential amperometry in combination with carbon fiber electrodes in urethane anesthetized Fmr1 mice (1.5g/kg i.p.) was used to explore DA transmission. Electrical stimulation of the DN (20 pulses; 50 Hz every 60 sec) elicited DA release in all aspects of the striatum and NAc that were explored. Expected results based on preliminary findings suggest significant differences between the Fmr1 wildtype and knockout strains in the DMS, NAcc and NAcsh, however no difference was found in the DLS. The current findings suggest influence of aberrations in the DN-striatal and DN-NAc pathways with regards to the cognitive and behavioral deficits seen in Autism.

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Poster

625. Executive Function: Models of Disorders

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Program#/Poster#: 625.16/Z21

Topic: F.02. Animal Cognition and Behavior

Title: Effect of sub-anesthetic ketamine on behavior in Cynomolgus Macaques

Authors: *G. J. DEMARCO[1], X. CHEN[1], B. DEREK[2], C. CHRISTOFFERSEN[2]; [1]Comparative Med., [2]Neurosci. Res. Unit, Pfizer Inc., Cambridge, MA

Abstract: Sub-anesthetic ketamine, a non-selective NMDAR antagonist, has been reported to induce hallucinatory-like behaviors in rhesus and squirrel monkey. The purpose of this study was

to test the hypothesis that sub-anesthetic ketamine would induce hallucination-like behaviors in Cynomolgus monkey. Animals were video-recorded for 20 min pre-dose, chaired for drug administration, immediately returned to their home cage and videoed for approximately 30 min. Captured video was reviewed and scored by a trained scientist using an in-house NHP Behavioral Scoring System. Ketamine at 0.05-0.3 mg/kg IV induced significant transient behavioral changes including extinguishing stereotypic behaviors and increased staring, self-inspection, star gazing, grooming, lipsmacking and gum chewing. At doses of 0.5 and 1.0 mg/kg IM ketamine induced significant sedation and ataxia which obscured many behaviors. These data suggest the behavioral response to sub-anesthetic ketamine in Cynomolgus Macaques is distinct from other monkeys and may represent a species specific form of hallucination-like behaviors.

Disclosures: G.J. DeMarco: A. Employment/Salary (full or part-time):; Pfizer Inc. **X. Chen:** A. Employment/Salary (full or part-time):; Pfizer Inc. **B. Derek:** A. Employment/Salary (full or part-time):; Pfizer Inc. **C. Christoffersen:** A. Employment/Salary (full or part-time):; Pfizer Inc..

Poster

625. Executive Function: Models of Disorders

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 625.17/Z22

Topic: F.02. Animal Cognition and Behavior

Title: Biting the hand that feeds you: Heart rate variability as a correlate of aggression

Authors: *L. A. CRAIG, E. P. WIERTELAK, J. E. MEYERS-MANOR;
Macalester Col., Saint Paul, MN

Abstract: Canine aggression affects many, with nearly 5 million dog bites reported each year in the United States alone. It is of considerable interest to determine the physiological factors that may lead to aggression and could be targeted for treatment. One factor that has been used in order to measure autonomic nervous system (ANS) function and inhibitory control is heart rate variability (HRV), the beat-to-beat change in the heart rate. Low HRV has been associated with impaired emotional and behavioral regulation and stress in both humans and animals and may reflect the balance between sympathetic and parasympathetic activation.The present study examined HRV differences between dogs with bite histories and dogs without bite histories using a Polar H7 heart rate monitor that was applied to subjects (male and female adults) at rest. Significantly lower HRV was found in the aggressive group. These results suggest that aggressive dogs may have physiological differences that reflect ANS dysregulation, which could

influence aggressive reactivity. Understanding these differences may be useful in order to develop and assess treatments for canine aggression.

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Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant DA024635

Title: Methamphetamine withdrawal inflates reward valuation by enhancing corticostriatal plasticity

Authors: ***A. B. THOMPSON**[1], A. STOLYAROVA[1], Y. ZHUANG[2], F. GOMEZ-PINILLA[3], A. IZQUIERDO[1];
[1]Psychology, [2]Integrative Biol. and Physiol., [3]Integrative Biol. and Physiology, Neurosurg., UCLA, Los Angeles, CA

Abstract: Exposure to drugs of abuse can induce changes in choice behavior that persist long into protracted withdrawal and abstinence. These changes include increased valuation of rewards and an enhanced ability to learn from positive feedback (Stolyarova et al. 2014, 2015), which may contribute to reinstatement of drug-seeking behavior when drug use is an option. Increased reward valuation after withdrawal may represent a successive positive contrast effect, in which responses to obtain reward are invigorated when reward value is unexpectedly increased. A recent computational model proposes that increased effort expenditure for rewards can occur when opportunities for reward procurement are presented to an animal with a belief that it is in a reward-impoverished environment (McNamara et al. 2013). Learning about the environment requires plasticity in corticostriatal pathways which link motor programs to outcomes. Brain-derived neurotrophic factor (BDNF) is released in the striatum by cortical afferents in an activity-dependent manner, where it signals through the TrkB receptor and interacts with dopamine to induce LTP at cortical inputs active during reward procurement (Altar et al. 1997, Jia et al. 2010, Wickens et al. 1996). In this way, conditions in the environment when TrkB signaling is elevated can influence subsequent behavior by changing an animal's belief about its environment. During withdrawal, negative somatic and psychological conditions may be 'stamped in' to the animal's memory, allowing for positive contrast effects and increased reward

valuation during protracted abstinence. We measured phosphorylation of the TrkB receptor (pTrkB) via western blot in the striatum of male Long-Evans rats (n=40) after methamphetamine. Tissue was collected either immediately after methamphetamine experience (escalating doses, culminating at 6.0 mg/kg over 2 weeks) or six weeks after the last dose. Expression of pTrkB was elevated in the immediate group, but had returned to baseline after six weeks, suggesting that a transient window of corticostriatal plasticity is opened during withdrawal from methamphetamine. A separate group of rats (n=14) was treated with the same dosing regimen then tested on a cognitively effortful 3-way visual discrimination task. Methamphetamine-, but not saline-treated rats, were able to learn the task to an 85% criterion, providing functional evidence of this enhanced plasticity. Experiments are designed to assess the effects of withdrawal on effort-based reward seeking behavior and uncover neural substrates.

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Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Support: Drexel Ventures Innovation Fund

Title: Investigating the role of catecholamines in cognitive dysfunction associated with Parkinson's disease

Authors: ***S. L. SIMMS**[1], L. KEIBEL[1], V. VELLA[2], J. S. SHUMSKY[1], B. D. WATERHOUSE[1], S. KORTAGERE[2];
[1]Neurobio. and Anat., [2]Microbiology and Immunol., Drexel Univ. Col. of Med., Philadelphia, PA

Abstract: Parkinson’s disease (PD) is a progressive neurodegenerative disorder that produces debilitating motor and cognitive impairments. The disease is characterized by a loss of dopaminergic neurons in the substantia nigra, and a subsequent reduction of dopamine and norepinephrine levels throughout the brain. The influence of dopamine deficiencies on motor disturbances has been well-studied. However, its effect on cognitive performance has not been well characterized. We have previously investigated the role of catecholamines, particularly norepinephrine and dopamine, in facilitating cognitive function in naïve animals. We designed

the compound, SK609, with dual activity as a selective dopamine D3 receptor agonist and a norepinephrine transporter reuptake inhibitor. In naïve animals tested on a sustained attention task, SK609 improved performance similar to the psychostimulant methylphenidate (MPH - Ritalin®). This improvement could be reversed with the D2/D3 receptor antagonist raclopride as well as the alpha-1 adrenergic receptor antagonist prazosin, implicating both dopaminergic and noradrenergic mechanisms. Conversely, naïve animals tested on a task of flexible attention showed no difference in performance when treated with SK609. However, performance of the task was disrupted by raclopride, suggesting involvement of dopamine in mediating flexible attention. Given these findings, our present study investigated the effects of SK609 on the mild cognitive deficit observed in PD. Hemiparkinsonian rats were put through a battery of tests to assess sustained attention, flexible attention and working memory. In the attention set-shifting task, treatment with SK609 normalized performance of PD rats, which previously showed significant impairments in simple and reversal discriminations relative to naïve animals. By contrast, in a cross maze task of working memory, animals treated with SK609 displayed impaired performance relative to naïve controls, a result consistent with the reported actions of other dopamine receptor agonists. While these outcomes suggest some potential therapeutic value for SK609 in treating Parkinson's cognitive deficits, they also indicate that dopamine's involvement in executive functions is task-dependent. Furthermore, our finding that SK609 selectively modulates sustained and flexible attention tasks suggests that different catecholaminergic pathways could be mediating these cognitive tasks.

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Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Support: Michael J. Fox Fdn.

USPHSGs #NS087559

USPHSGs #DA033121

Title: Chronic pramipexole treatment influences motor and impulse control in a rat model of Parkinson's disease

Authors: *S. TEDFORD[1], N. A. HOLTZ[1], S. A. GRASSO[1], A. L. PERSONS[1], T. C. NAPIER[1,2];
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Abstract: Pramipexole (PPX) is a dopamine agonist commonly used to treat motor disturbances observed in Parkinson's disease (PD). Subsets of treated patients develop impulse control disorders (ICDs), e.g., problem gambling. In hopes of providing more stable motor benefits, PPX has been prepared as an extended release formulation. The consequence of this formulation on ICD propensity is currently being studied. To advance this effort, we determined the effects of chronic PPX administration on motor function and risk-taking in a rat model of PD and ICDs. Rats with 6-OHDA-induced lesions of the dorsolateral striatum (to model PD) were implanted with stimulating electrodes in the lateral hypothalamus. This allows for an intracranial self-stimulation-mediated probability discounting task as measure of risk-taking to indicate ICDs. We used subcutaneously implanted osmotic minipumps to continuously release PPX for 14 days. Discounting task outcomes were compared to the ability of PPX to improve lesioned-induced deficits in forelimb stepping adjustments, a task that emulates PD-like postural instability. We reveal that within 24hr of pump insertion, motor deficits were fully reversed by 0.3, 0.6 and 1.2mg/kg/day PPX. These improvements occurred in all lesioned rats and were stable throughout the 14 day experimental timeframe. In contrast, discounting was not altered until several days of PPX exposure, and significance occurred only at the 1.2mg/kg/day dose. A subset of rats showed decreased discounting (i.e., increased risk-taking) at all doses tested. These results reveal the utility of a novel model of PD with ICDs wherein, like treated human PD patients, a subset of rats showed risk-taking behavior. These findings demonstrate the differential influence of PPX on motor benefits and ICD development.

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Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

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MGH/ECOR Scholar's Fund

Title: Rodent models of delirium and encephalopathy: Behavioral and neurophysiological studies in aging

Authors: *E. Y. KIMCHI[1,3], B. F. COUGHLIN[2], S. S. CASH[2,3];
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Abstract: Delirium is an acute disturbance of attention and awareness commonly seen in elderly patients. Delirium heralds the possibilities of not only sustained brain dysfunction but also dependence and death. Epidemiologic studies have suggested that the most prominent predisposing risk factors for delirium are aging and dementia and that common precipitating risk factors include anticholinergic medications, inflammation, and anesthesia. We are developing animal models of delirium by studying the responses of aged (22-26 months) vs. young (3-6 months) rats to specific risk factors in order to determine the causal significance of each risk factor. We have developed a translational, rodent version of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) scale, used to assess delirium in patients unable to give a verbal response (such as intubated patients). We evaluate delirium phenotypes using simultaneous measurements of electrophysiology, discrimination behavior, and locomotor activity. Both scopolamine and lipopolysaccharide (LPS) injections cause EEG changes consistent with slowing seen in clinical delirium: increased power at lower frequencies and decreased power at higher frequencies (n=18 scopolamine, n=10 LPS). Both scopolamine and LPS injections also cause decreased discrimination accuracy on a flexible Go/Nogo auditory discrimination, consistent with impaired attention. Scopolamine increases locomotor activity consistent with a hyperactive delirium phenotype, whereas LPS decreases locomotor activity, consistent with a hypoactive delirium phenotype. Our results demonstrate that aged rodents display the expected core translational features of delirium, providing evidence that animal models are likely to generate testable, clinically relevant hypotheses about the pathophysiology of delirium.

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Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Support: Ministry of Science and Technology, Taiwan

Title: Voluntary physical exercise improves the subsequent motor and cognitive impairments in Parkinson's disease model of rats

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Abstract: Parkinson's disease (PD) is typically characterized by the impairments of motor function. Gait disturbances similar to those of human PD can be observed in animals after injection of neurotoxin 6-hydroxydopamine (6-OHDA) to induce unilateral nigrostriatal dopamine depletion. Exercise has been shown to be a promising non-pharmacological approach to reduce the risk of neurodegeneration disease. In this study, we investigated the long-term effects of voluntary running wheel exercise on gait phenotypes, rotational behavior as well as histology in a 6-OHDA-lesioned rat model of PD. In results, we observed that five weeks voluntary exercise alleviates and postponed the 6-OHDA induced gait deficits, as compared to non-exercise controls, including a significantly improved walking speed, step/stride length, base of support and print length. However, the rotational behavior and tyrosine hydroxylase (TH)-positive neurons in the substantia nigra in exercise group did not show significant differences when compared with non-exercise group. In conclusion, we first analyzed the detailed changes of gait pattern to investigate the potential benefits after long-term exercise in the rat model of PD, which could be useful for future objective investigation of locomotor function in PD or other neurological animal models. Also, these results suggest that long-term voluntary exercise reduces the aggravation of motor symptom but not exerts neuroprotection in PD rats model, which might be might be relevant for the development of potential treatment protocols for functional recovery in PD.

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Poster

625. Executive Function: Models of Disorders

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Title: High midbrain D3 receptor availability is related to inflexible decision-making processes in rats

Authors: *S. M. GROMAN[1], N. J. SMITH[1], J. R. PETRULLI[2], L. CHEN[1], B. MASSI[3], D. LEE[4], E. D. MORRIS[2], J. R. TAYLOR[1];
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Abstract: Decision-making processes are impaired in individuals with psychiatric disorders, such as addiction and schizophrenia. Converging evidence indicates that dysfunction of the dopamine D2/3 receptor underlies the inflexible, impulsive decisions that are observed in individuals with psychiatric disorders. However, it is unclear whether these behavioral effects are due to disruptions in the D2, the D3 or both receptor systems. To address this question, flexible decision-making processes were assessed in rats using a three-choice spatial discrimination and reversal task and compared to PET measurements of D3 receptor availability. Thirteen adult, male rats were trained to acquire and reverse three-choice spatial discrimination problems that were probabilistically reinforced (PRL). Choice behavior of rats was characterized using previously validated computational models to estimate learning rates and outcome sensitivity for each individual rat. PET scans, using the radioligand [11C](+)PHNO, were collected in the same rats to quantify D2/3 receptor availability in the dorsal striatum and midbrain and related to the behavioral performance of rats in the PRL task. [11C](+)PHNO binding potential in the midbrain, an area rich in D3 receptors, was related to the performance of rats in the reversal, but not the acquisition, phase of the PRL. Rats with greater midbrain [11C](+)PHNO binding potential (BPND) had more difficulty reversing a spatial discrimination and made more perseverative responses than rats with less [11C](+)PHNO BPND. Furthermore, midbrain [11C](+)PHNO BPND was inversely related to the learning rate and the sensitivity of rats to positive, but not negative, outcomes following a reversal. These data demonstrate a new role for midbrain D3 receptors in select aspects of reinforcement learning and suggest that individual variation in D3 receptors regulates flexible behavior. These results add to a growing body of work suggesting that midbrain D3 receptor abnormality may underlie the behavioral problems

observed in psychiatric disorders and implicate the D3 receptor as a target for the treatment of disorders that are associated with decision-making impairments.

Disclosures: **S.M. Groman:** None. **N.J. Smith:** None. **J.R. Petrulli:** None. **L. Chen:** None. **B. Massi:** None. **D. Lee:** None. **E.D. Morris:** None. **J.R. Taylor:** None.

Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Title: Response of medial prefrontal cortex to cues for behavioral restraint

Authors: *K. MANSON[1], J. D. ROITMAN[2];
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Abstract: Environmental cues associated with rewards often prompt approach and consummatory actions that are difficult to override, even when restraint may lead to beneficial outcomes in the short- or long-term. The medial prefrontal cortex (mPFC) has been implicated in directing reward/value-based choices and dysfunction of the PFC has been extensively associated with impulsive actions. Control of goal-directed behavior may be executed through mPFC connections with the nucleus accumbens (NAc), which integrates information about environmental cues and rewards to influence motor behaviors via basal ganglia circuitry. The role of excitatory neural activity within PFC to engage inhibitory processes over approach behavior is still unclear. Recently, Roitman and Loriaux (2014) found greater increases in NAc neuronal firing when animals restrained behavioral action in a symmetric Go/NoGo task in which all correct responses – Go and NoGo – were rewarded. Animals' ability to restrain their approach behavior is substantially reduced when glutamatergic AMPA/kainate, but not NMDA, receptors are pharmacologically blocked in NAc, suggesting that excitatory inputs to the NAc allow the animal to inhibit approach behavior. We hypothesize that mPFC may serve as a source for this excitatory input. In support of this, bilateral inactivation of mPFC activity and disconnection of mPFC communication with NAc caused an increase in NoGo errors in the symmetric Go/NoGo Task (Manson et al. *In Prep*). To examine whether mPFC neuronal responses differentially encode Go and NoGo cues that are both reward-predictive, but require either approach or restraint, we implanted electrode arrays in the mPFC and recorded the activity of multiple single neurons while rats performed the Go/NoGo task. Neurons in mPFC showed transient responses at the onset of cues that were modulated by cue type and behavioral response.

These results support a role for mPFC providing a source of signaling for restraint of behavior in response to environmental cues.

Disclosures: K. Manson: None. **J.D. Roitman:** None.

Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

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Title: Effects of methylphenidate on prefrontal cortex and decision-making throughout development

Authors: *J. D. ROITMAN[1], E. JACOBS-BRICHFORD[2], M. MCMURRAY[2], C. SHORT[2], L. AMODEO[2];
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Abstract: The psychostimulant compound, methylphenidate (MPH) is the most common treatment for ADHD, and is approved for administration to children in the US. At therapeutic doses, MPH treatment has been shown to reduce the severity of the core symptoms in ADHD, including cognitive impulsivity, without increasing an association with subsequent substance abuse. However, due to its wide availability, MPH is also one of the more highly misused and abused drugs in adolescence, in both clinical and general populations. Given that MPH works through the same pathways activated by other drugs of abuse, it is not surprising that the focus of the MPH literature is related to the potential risk of future drug addiction. However, the possible short and long-term effects of MPH on decision-making are not clearly understood. The goal of this research was to examine MPH actions on decision-making during a critical developmental period. Long-Evans rats (non-hyperactive) were injected with MPH (0, 1, 2.5, or 5 mg/kg IP) twice daily throughout late adolescence (PD35-50). During this period, rats performed Magnitude Discrimination and Delay Discounting tasks. In contrast to prior studies in hyperactive rats, we found that treatment with MPH did not decrease naturally impulsive behavior in normal (non-hyperactive) adolescent rats. After discontinuation of MPH, behavioral flexibility and risk-preference were subsequently assessed in adulthood. Behavioral flexibility was assessed using a Reversal Learning task, which revealed that animals previously treated with MPH showed improved acquisition, but no difference in reversal performance. Rats' preference

for probabilistic rewards/tolerance for reward omission was measured using a Risk Task in which they chose between small-certain and large-risky options. In this task, rats treated with MPH in adolescence showed increased risk preference in adulthood. Taken together, the results suggest that adolescent MPH-induced increases in risk-preference were not due to increased perseverative behavior. To determine whether these effects may be due to changes in dopaminergic signaling in prefrontal cortex, we quantified mRNA expression of D1 and D2 receptors in the orbitofrontal cortex (OFC) using qPCR. Results suggest a shift in the balance of D1/D2 receptor expression in the OFC of MPH-exposed rats. Overall these findings suggest that MPH administered during late adolescence can affect cognitive outcomes in adulthood.

Disclosures: J.D. Roitman: None. **E. Jacobs-Brichford:** None. **M. McMurray:** None. **C. Short:** None. **L. Amodeo:** None.

Poster

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ANR

Title: Neural markers of cognitive control, and their evolution during a pre-symptomatic monkey model of Parkinson's disease

Authors: *C. R. WILSON[1,2], F. STOLL[1,2], M. C. M. FARAUT[1,2], J. VEZOLI[1,2,3], V. LEVIEL[1,2], E. PROCYK[1,2];
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Abstract: Beta oscillations (15-30Hz) are associated with top-down cognitive control, and modulated in Parkinson's disease (PD). We investigated whether frontal beta oscillations are differentially modulated by different parameters contributing to cognitive control, including exploration vs. exploitation, and time on the task, in 2 macaque monkeys. We then used these data as a baseline to characterize the progressive alteration of behavioural and electrophysiological markers under systemic dopaminergic system lesion, using a chronic low dose MPTP treatment in a longitudinal study. This approach contributes fundamental knowledge about the dopamine system in cognitive control, but in addition the detection of alterations in cognition or underlying neurophysiological mechanisms prior to the onset of the motor symptoms in PD constitutes a crucial prerequisite for the development of early diagnostic tools. The monkeys learned the Problem Solving Task by searching (SEA phase) amongst targets to find the target rewarded with juice, and then repeating that choice for several trials (REP phase). Problems were separated by a clear change signal, restarting the search phase. The contrast between SEA and REP phases provides an index of cognitive control. Monkeys were chronically implanted with at least 22 electrodes resting on the dura mater to provide electroencephalographic (ECoG) recordings. During a stable control period, frontal beta power was modulated both by cognitive control demands in the SEA and REP phases of the task, and also by within-session progression towards a final large bonus reward. Importantly, when the monkey spontaneously paused for several minutes during the session, these beta power modulations were reset. Feedback related potentials (FRPs) over medial frontal cortex differentiated the forms of feedback necessary for behavioural adaptation in the task. Monkeys then received a slow low-dose MPTP treatment whilst continuing to provide ECoG recordings and behaviour. Monkeys remained below the threshold for clinically significant motor symptoms throughout. FRPs were significantly modulated by MPTP treatment, to the point that they no longer reflected the contrast between correct and incorrect feedback, but despite this, cognitive performance was unchanged. Beta oscillatory power was maintained overall across treatment, and in contrast to the FRPs, beta power continued to reflect cognitive control. However, the within-session effect on beta power was diminished. Hence a slow dopaminergic lesion has contrasting effects on different neural markers of cognitive control.

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Poster

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Title: Pupillometric readouts of decision making in mice

Authors: *P. J. STEFFAN[1], M. MCGINLEY[2], D. LEE[3], D. MCCORMICK[2];
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Abstract: Pupillometry has been used extensively for over 50 years as a window into mental states and cognitive processes in human studies of decision making. The development of molecular-genetic tools to study brain circuits in mice has made them an attractive model system to study neural mechanisms of decision making. However, sophisticated behavioral paradigms for mice have been lacking and pupillometric readouts of decision making remain unexplored. We recently developed a psychometric tone-in-noise detection task for head-fixed mice on a cylindrical treadmill and used pupillometry to measure arousal. We found that the pupil diameter immediately before each sound was highly predictive of the speed and accuracy of target detection, largely irrespective of locomotor state (McGinley et al., 2015). Pupillometry in humans is predominantly used to estimate latent cognitive variables (e.g., cognitive load; Beatty, 1982) based on task-evoked pupillary responses, rather than baseline effects. Thus, we have analyzed task-evoked responses in our detection task. We find that pupils dilate differently for hits, misses, and false alarms. Hits aree associated with large (~7% increase; from baseline to peak) and persistent (lasting > several seconds) dilations. Misses have the smallest dilations (~2%) whereas false alarms are associated with intermediate dilations (~5%). Pupil dilations (width at half maximum) for misses and false alarms lasted ~2 seconds. These results show that task-evoked pupillary responses in mice are sensitive to choices and outcomes. To further explore the utility of pupillometry in mouse decision making we have developed a behavioral task in which mice make stay-leave valuation decisions, based on the widely-used 'patch-leaving' task in behavioral ecology (Stephens and Krebs, 1987). Mice initiate and terminate blocks of trials, termed 'patches,' with their locomotor activity on the treadmill. Within a patch, animals lick for sugar reward upon detection of target tones in a background noise stream. The reward volume decreases gradually in a patch and is reset upon entry to a new patch. This head-fixed virtual patch-leaving task may provide a framework to study ethologically-relevant, sophisticated decision making strategies, and their pupillometric readouts, in mice. Beatty, J (1982). Task-evoked pupillary responses, processing load, and the structure of processing resources. Psychol Bull, 91, 276-292. McGinley, MJ, David, SV, and McCormick, DA (2015). Cortical membrane potential signature of optimal states for sensory signal detection. (in review). Stephens, DW, & Krebs, JR (1987). Foraging Theory. Princeton University Press.

Disclosures: **P.J. Steffan:** None. **M. McGinley:** None. **D. Lee:** None. **D. McCormick:** None.

Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Title: Cocaine self-administration and incubation of craving exacerbates poor decision-making on a rat gambling task, exposing individual vulnerability to addiction

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Abstract: Maladaptive decision-making is commonly found amongst substance abusers and is thought to play an integral role in the development and maintenance of addiction. Indeed, human studies using the Iowa Gambling Task (IGT), a validated measure of decision-making, have found that substance dependent individuals tend to choose the least advantageous option and are less likely to change their strategy following losses compared to controls. These deficits have been found to worsen following withdrawal. Animal studies using self-administration have found that cocaine use impairs a variety of executive functions including reversal learning and impulse control. However, little preclinical work has examined whether cocaine self-administration or prolonged withdrawal has an impact on cost/benefit decision-making. More critically, no animal models have focused on individual differences in decision-making, which may underlie the likelihood to abuse drugs and relapse. To investigate this relationship, we trained male Long-Evans rats on a cued or uncued Rat Gambling Task (rGT), rodent analogues of the IGT. In brief, animals were allowed to choose between 4 different nosepoke holes of an operant box, each associated with a different sugar pellet reward (1-4 pellets), penalty time out (5-40s), and probability of receiving a reward over a penalty (0.9-0.4). The advantageous options (those resulting in 1 or 2 sugar pellets) are commonly chosen while the disadvantageous options (3 and 4 sugar pellets) are often avoided. The cued version of the rGT utilizes win-paired light and tone cues that intensify in number and variability as the reward won increases, a method which has been found to increase the choice of the disadvantageous options. Following training, rats were implanted with jugular vein catheters and were allowed to self-administer cocaine for 10 days followed by 30 days of withdrawal. Decision-making was simultaneously measured by rGT performance throughout the experiment. Results indicated that a subgroup of animals with a baseline preference for the disadvantageous options in both the cued and uncued versions of the task performed worse (i.e. chose the risky options more) following cocaine self-administration

and withdrawal, took greater amounts of cocaine, and had potentiated levels of responding for drug-paired cues following withdrawal. These data demonstrate that cocaine self-administration intensifies poor decision-making within a vulnerable subgroup, providing a model by which we can begin to investigate the individual susceptibility to abuse drugs and relapse.

Disclosures: **J.N. Ferland:** None. **C.A. Winstanley:** None.

Poster

625. Executive Function: Models of Disorders

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Topic: F.02. Animal Cognition and Behavior

Title: Pupillary dynamics reflect behavioral states in head-fixed rats performing whisker direction discrimination tasks

Authors: *B. SCHRIVER, S. BAGDASAROV, Q. WANG;
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Abstract: The use of pupillometry as a noninvasive means to gauge human behavior state has been well-established. In particular, change in pupil size has been successfully used as a reliable indicator of mental efforts, change in attention allocation, and arousal level in humans. However, little is known about the correlation between pupillary dynamics and behavioral states in awake, behaving rodents. We trained head-fixed rats to perform a whisker direction discrimination task using a Go/No-Go paradigm. The pupil of the rats was simultaneously imaged using a custom made infrared pupillometry system. The dorsal direction was selected as the Go direction (S+) while the ventral direction was the No-Go direction (S-). The rats preferentially responded to S+ at a probability of ~85% while responding to S- with a probability of only ~25%. The rejection rate of S- stimuli was dependent on their angular velocities. The higher the velocity, the less likely the animal rejected S- Stimuli. For S+ stimuli the response time decreased with increasing velocity. Pupillometry data showed that the pupil of the rats dilated for all behavior outcomes, i.e. Hit, Correct Rejection, False Alarm, and Miss. However, the pupil dilated approximately 3 times larger for Hit trials than for False Alarm or Miss trials. Furthermore, the baseline pupil size is tightly correlated with the behavioral performance. Specifically, the False Alarm trials had the largest baseline pupil size while the Miss trials had the smallest baseline pupil size. The baseline pupil sizes for both the Hit and Correct Rejection trials were around average. More interestingly, the pupillometry data, when aligned with stimulus onset for the miss trials, showed that the pupil began to dilate prior to the window of opportunity closing. This suggests that the pupil dilation is

not due to motor output. Our preliminary data also demonstrated that the pupil dynamics are dependent on the behavioral outcome of previous trials. Taken together, our data suggest that, similar to human subjects, pupillary dynamics in awake behaving rats are a reliable indicator of their behavior state.

Disclosures: **B. Schriver:** None. **S. Bagdasarov:** None. **Q. Wang:** None.

Poster

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Topic: F.02. Animal Cognition and Behavior

Title: Assessing cognitive flexibility in the social home-cage

Authors: *T. J. BURTON[1,2], A. SAWATARI[2];
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Abstract: "Cognitive Flexibility" is an Executive Function that allows an organism to inhibit previously learned strategies or rules that are no longer currently relevant so that new and appropriate patterns of behaviour can be developed and applied. This process of adapting to changes in the environment is compromised in patients with neuropsychiatric disorders such as schizophrenia and Alzheimer's disease. Much is still unknown about the mechanisms that control complex and integrative higher order functions in the brain. Traditionally, assays of cognitive flexibility in the rodent have been conducted in the cross maze, where rats can be trained to use egocentric response strategies, allocentric spatial strategies or visual cues to guide choice behaviour. While much has been learned about the neural circuitry underlying executive function using this approach, these paradigms are labour intensive, require regular operator-animal interaction and necessitate animals to be removed from their home cage and social setting. These latter two features can be sources of unwanted stress and anxiety which may interfere with normal behaviour. Developing more naturalistic and species-relevant behavioural tasks is essential for improving our understanding of intact and disordered neural systems. Using the IntelliCage system for mice, we have developed a novel and fully automated method for investigating cognitive flexibility in the home cage - a more naturalistic social setting for this species than a cross maze or operant box. Mice were required to learn one of two tasks (either a Visual cue-Dependent [VD] task or a Response-Dependent [RD] task) before the task contingencies were changed (either an Extradimensional Shift [EDS; between-task switch] or a Rule Reversal [RR; within-task change]). Robust learning was observed in both the VD and RD

tasks. However, the RD task was acquired more rapidly than the VD task. A significant reduction in performance was observed for all animals immediately after the task contingencies were changed. Moreover, these particular results were remarkably consistent with theoretical expected performances after such task changes. This automated approach also allowed for a detailed examination of the evolution of choice behaviour during all phases of learning and adaptation to contingency changes. We show that the IntelliCage is a promising tool for developing reliable and species-relevant assays of specific cognitive functions in mice.

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Poster

626. Learning and Memory: Hippocampal Circuits

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Title: ΔFosB regulation of hippocampal physiology and learning

Authors: *A. L. EAGLE[1], P. A. GAJEWSKI[2], M. YANG[1], P. J. KENNEDY[3], H. WANG[1], A. J. ROBISON[1];
[1]Dept. of Physiol., [2]Genet. Program, Michigan State Univ., East Lansing, MI; [3]Dept. of Psychology, UCLA, Los Angeles, CA

Abstract: The hippocampus (HPC) is essential for memory consolidation, a process dependent on synaptic plasticity and gene expression in HPC neurons. However, the transcriptional machinery underlying HPC-dependent learning has yet to be wholly delineated. The transcription factor ΔFosB is induced throughout the brain by chronic exposure to drugs or stress and regulates synaptic plasticity in the nucleus accumbens (NAc), suggesting it drives activity-dependent gene expression, but the role of HPC ΔFosB in plasticity and learning is currently unknown. Here, we find that ΔFosB is induced in HPC by spatial learning, suggesting it may be important for transcription-dependent changes in HPC synaptic plasticity associated with learning. We used viral tools to demonstrate that HPC-targeted ΔFosB inhibition in mice impairs

HPC-dependent learning and memory. Interestingly, HPC ΔFosB viral overexpression also impairs HPC-dependent learning and memory. We also demonstrate here that ΔFosB overexpression increases immature dendritic spines on HPC CA1 pyramidal cells. Ongoing studies are currently investigating the role of ΔFosB in synaptic and cellular physiology, as well as downstream gene targets of ΔFosB. These findings suggest that endogenous ΔFosB is crucial for normal HPC function and that cell-specific ΔFosB expression is required for memory formation, while general overexpression introduces noise that prevents establishment of a memory trace. Finally, these data support the hypothesis that ΔFosB exerts its behavioral effects through modulation of HPC synapses, and ongoing studies will address this hypothesis directly.

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Poster

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Support: Whitehall Foundation Research Grant Award (APP131146)

Title: Epigenetic regulation of the FosB gene in hippocampus

Authors: ***P. A. GAJEWSKI**[1], A. L. EAGLE[2], E. A. HELLER[3], I. MAZE[4], A. J. ROBISON[2]; [1]Genet., [2]Physiol., Michigan State Univ., East Lansing, MI; [3]Neurosci., [4]Pharmacol., Mount Sinai Sch. of Med., New York, NY

Abstract: Elucidation of the molecular mechanisms of memory formation is critical for the development of a cohesive theory of memory. However, the patterns of gene regulation that occur during learning remain unknown. Consolidation of explicit memories occurs through synaptic plasticity in the hippocampus, and some of the molecular mechanisms of this process are well characterized, but epigenetic regulation underlying changes in hippocampal gene expression and the distribution of gene expression through the hippocampus is poorly understood. The transcription factor DeltaFosB is an important arbitrator of activity-dependent gene expression in nucleus accumbens (NAc) underlying maladaptive changes in reward processing. Previous studies demonstrate that drugs of abuse and stress also upregulate DeltaFosB in hippocampus, but its role in this brain region is uncharacterized. Here, we demonstrate for the first time that DeltaFosB is upregulated in the dorsal hippocampus in

response to novel environment exposure, spatial learning, and cocaine exposure, and we are currently determining whether the expression pattern of DeltaFosB differs throughout hippocampal subregions. Furthermore, we use chromatin immunoprecipitation to demonstrate that dimethylation of lysine 9 at histone H3, a repressive histone modification, is decreased at the FosB gene promoter in hippocampus after exposure to either cocaine or a novel environment. Studies are ongoing to examine the effects of learning and drug exposure on other histone modifications, such as acetylation of lysine 9, as well as global levels of histone modifications in hippocampus. Furthermore, experiments using viral-mediated gene expression are ongoing to investigate the relationship between these histone modifications and DeltaFosB expression and learning behavior. These findings collectively suggest that specific salient stimuli, such as spatial learning or drug exposure, induce epigenetic changes in the hippocampal FosB gene promoter that regulate DeltaFosB induction, which in turn may control the transcription of genes that underlie hippocampal cell function, plasticity, and learning.

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Poster

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Title: Hippocampal Arc protein expression in male C57BL/6J mice is exploration dependent in the novel object recognition task

Authors: *D. A. CINALLI, JR[1], S. J. COHEN[2], R. W. STACKMAN, Jr.[2];
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Abstract: Transcription and translation of proteins are required for the consolidation of episodic memory. Arc, an effector immediate early gene, has been linked to synaptic plasticity which occurs following learning and memory. It is well established that the rodent hippocampus is essential for processing spatial memory, but its role in processing object memory is a point of contention. This study seeks to elucidate hippocampal processing of object memory using the Novel Object Recognition (NOR) task. Using immunohistochemical techniques, we stained for arc proteins in pyramidal neurons in the CA1 region of the dorsal hippocampus in C57BL/6J

mice following two variations of the NOR task. Mice were placed into a familiar high-walled square enclosure that contained two novel 3D objects during the sample session. During the test session 24 h later, one of the objects was replaced with a novel object. Results of arc-positive neuron counts suggest that in mice that accumulated 30s of exploration of each object during the sample session, a substantial hippocampal ensemble was activated. In contrast, in mice that accumulated only 10s of exploration on each object during the sample session, hippocampal activation was not significantly different from controls that were not exposed to any objects. Arc expression was also examined in neurons of other hippocampal subregions, as well as in medial temporal lobe cortical regions such as the perirhinal cortex. Taken together, these results suggest that the mice must acquire a threshold amount of object information during the sample session before the hippocampal CA1 region is engaged in object memory processing. These data support that the view that the rodent hippocampus processes object memory.

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Poster

626. Learning and Memory: Hippocampal Circuits

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Title: Involvement of hippocampal diaschisis in mediating stroke-induced hippocampal hypofunction and memory deficits

Authors: ***G. RABILLER**[1], Y. NISHIJIMA[2], J.-W. HE[2], X. LEINEKUGEL[1], V. ANDJELKOVIC[1], A. HAMBUCKEN[1], B. BONTEMPI[1], J. LIU[2];
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Abstract: The cognitive consequences and the underlying mechanisms leading to cognitive impairments after cerebrovascular occlusive diseases are still unclear. In addition to the infarct zone that suffer the deadly consequence of ischemic stroke, the penumbra surrounding the lesion site and some brain regions remote to the ischemic areas can be functionally affected by the insult. This phenomenon is referred to as diaschisis. In light of the importance of interactions between hippocampus and cortex during memory processing, we hypothesized that the cognitive impairments observed following ischemic stroke could occur in the absence of direct

hippocampal insult, possibly via impaired connectivity within cortico-hippocampal networks leading to diaschisis-induced hypofunctioning in specific hippocampal subregions. To test this possibility, we used the distal middle cerebral artery occlusion (dMCAO) in rats which induces restricted cortical infarct in the somatosensory (SS) cortex in the absence of direct hippocampal injury. dMCAO rats exhibited reduced expression of the activity-dependent gene c-fos in the hippocampus when exploring a novel environment, indicating neuronal hypoactivation. Some of these rats also exhibited impaired associative olfactory memory when tested in the social transmission of food preference (STFP) task. To confirm that the ischemic-induced hippocampal hypofunctioning resulted from reduced afferent inputs (i.e. deactivation) originating in the damaged cortex, we performed region-specific pharmacological inactivation of SS and entorhinal cortices using the sodium channel blocker lidocaine or the AMPA receptor antagonist CNQX. Fos imaging revealed that these treatments induced hippocampal hypoactivation and impaired memory performance as measured in the STFP task. We additionally recorded hippocampal activity in anesthetized rats during acute stroke or after SS cortex inactivation and found an increase in the occurrence of ripples during reperfusion after stroke and a shift of the theta phase between the hippocampus and cortex, suggesting alteration in the dynamics of hippocampal-cortical interactions. Taken collectively, these findings identify hippocampal diaschisis as a crucial mechanism for mediating stroke-induced hippocampal hypofunction and associated memory deficits.

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Poster

626. Learning and Memory: Hippocampal Circuits

Location: Hall A

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Topic: F.02. Animal Cognition and Behavior

Support: NSF INSPIRE

Title: The design and application of a flexible parylene-based multi-electrode array for *in vivo* recording from the rat hippocampus

Authors: ***H. XU**, M.-C. HSIAO, D. SONG, T. W. BERGER;
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Abstract: The hippocampus is a deep brain structure critical for the formation of new long-term declarative memories. Hippocampal malfunctions can be caused by various diseases and pathological conditions. The hippocampus is anatomically composed of three main sub-regions, i.e., dentate gyrus, CA3 and CA1. Lesion studies have indicated that damages to different sub-regions of the dorsal hippocampus of rats can result in distinct impairments in detecting spatial novelty. Because of the regular intrinsic connections within the hippocampus and the highly structured anatomical organization of the hippocampus sub-regions, it has become a model structure for the studies of cognitive functions in particular and various forms of synaptic plasticity in general. Understanding how the hippocampus is involved in declarative memory and studying its neural plasticity require simultaneous recordings of neural activities from multiple sub-regions of the hippocampus in behaving animals. Parylene C is a highly biocompatible and flexible polymer. Based on histological results from brain slices and neural activities recorded from behaving animals, we have designed a multi-shank electrode which uses Parylene C as base and has multiple recording sites specifically positioned along the longitudinal axis to conform to the curvy shape of the rat hippocampus. This Parylene probe can be implanted into the rat hippocampus for multi-site chronic recordings of unitary activities. Spike trains from multiple sub-regions of the hippocampus will be recorded and examined under complex behavioral conditions. Responses of single cell activities to the manipulation of spatial cues as well as neural functional connectivities will be investigated to identify the roles of hippocampus sub-regions in spatial information processing.

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Poster

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Topic: F.02. Animal Cognition and Behavior

Support: Cluster of Excellence Cellular Networks

Interdisciplinary Center for Neurosciences

Title: Consequences of altered dendritic arborization in hippocampal networks -linking molecular signaling and neuronal morphology

Authors: J. MAURER[1], D. MAUCERI[2], H. BADING[2], A. DRAGUHN[1], *M. BOTH[1];
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Abstract: Dendrites of neurons receive multiple synaptic inputs and transmit information to the soma. Thus, they provide powerful options for active modulation and integration of signals arriving at different dendritic segments. The morphology of dendrites plays a crucial role in this context. Here, we investigate alterations of information processing due to dendritic arborization changes in mouse hippocampal CA1 pyramidal cells. Previous findings showed that the vascular endothelial growth factor D (VEGFD) is involved in the maintenance of dendritic arborization. After downregulation of VEGFD in hippocampal neurons, a reduction in the length and the complexity of basal dendrites was observed (Mauceri et al., 2011)1. We have studied the role of VEGFD for arborization and synaptic input to basal and apical dendrites of CA1 pyramidal neurons. Following suppression of the growth factor, we performed 3D reconstructions of apical and basal dendritic trees (covering stratum oriens, stratum radiatum and stratum lacunosum-moleculare). In line with the former findings, basal dendrites became shorter and less complex. Surprisingly, we found no hint for similar changes in apical dendrites. Preliminary data do even indicate increased dendritic arborization in stratum lacunosum-moleculare. Passive membrane properties and action potential firing were unchanged. In summary, these findings indicate a shift in the balance of synaptic inputs to CA1 pyramidal cells following downregulation of VEGFD. Regulation of dendritic morphology by VEGFD follows different mechanisms in apical and basal dendrites, suggesting specific effects of this growth factor on input integration in the hippocampal network. ___ 1 Mauceri D, Freitag HE, Oliveira AM, Bengtson CP, Bading H (2011) Nuclear calcium-VEGFD signaling controls maintenance of dendrite arborization necessary for memory formation. Neuron. 71(1):117-130

Disclosures: **J. Maurer:** None. **D. Mauceri:** None. **H. Bading:** None. **A. Draguhn:** None. **M. Both:** None.

Poster

626. Learning and Memory: Hippocampal Circuits

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Title: Disruption of the hippocampal gabaergic system in the fgf14–/– mouse model

Authors: *T. K. ALSHAMMARI[1,3], M. A. ALSHAMMARI[1,3], E. HOXHA[4], M. N. NENOV[1], M. CAMBIAGHI[4], A. MARCINNO[4], T. F. JAMES[2], J. LI[5], B. SACCHETTI[4], H. Y. MELTZER[5], F. TEMPIA[4], F. LAEZZA[1];
[1]Pharmacol. and Toxicology, [2]Dept. of Neurosci. and Cell Biol., Univ. of Texas Med. Br., Galveston, TX; [3]King Saud Univ. Grad. Studies Abroad Program, King Saud Univ., Riyadh, Saudi Arabia; [4]Dept. of Neurosci., Univ. of Torino, Torino, Italy; [5]Dept. of Psychiatry and Behavioral Sci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL

Abstract: The balance between excitation and inhibition in the brain is highly dependent on the functional integrity of gamma-amino-butyric acid (GABA)-releasing interneurons. Though these cells represent only ~ 20% of all neurons in the CNS, they exert a powerful activity in the brain by synchronizing principal neuron output. Studies indicate that aberrant function of GABAergic interneurons especially parvalbumin (PV) interneurons is strongly associated with cognitive deficits in psychiatric disorders. However, the mechanisms leading to GABAergic interneurons dysfunction in the brain disease context are not yet completely understood. Here, we show that fibroblast growth factor 14 (FGF14), a component of the voltage-gated Na+ channel complex and a regulator of the presynaptic neurotransmitter release machinery, plays a critical role in regulating structure and function of GABAergic interneurons. In Fgf14-/- animals we found that the total number of PV interneurons in the CA1 hippocampal region is reduced significantly and that these changes are associated with a reduction in the expression of synaptic GABAergic markers. These phenotypes coincide with alterations in the CA1 inhibitory tone, reduction of *in vivo* gamma frequency oscillations and working memory deficits. Bioinformatics analysis of schizophrenia transcriptomics reveals functional co-clustering of FGF14 and genes enriched within the GABAergic pathway along with correlative reduced expression of FGF14, glutamic acid decarboxylase 67 (GAD67) vesicular GABA transporter (VGAT) in the disease context. This study highlights a new potential role of FGF14 in regulating the excitation/inhibition tone in the filling knowledge gaps in mechanisms underlying cognitive dysfunction in neuropsychiatric disorders.

Disclosures: T.K. Alshammari: None. **M.A. Alshammari:** None. **E. Hoxha:** None. **M.N. Nenov:** None. **M. Cambiaghi:** None. **A. Marcinno:** None. **T.F. James:** None. **J. Li:** None. **B. Sacchetti:** None. **H.Y. Meltzer:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Activas, the American Foundation for Suicide Prevention, Auspex, Forum, Janssen, Mag T Therapeutics, Naurex, Reviva, Sumitomo Dainippon, Sunovion. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds);

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Poster

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Topic: F.02. Animal Cognition and Behavior

Support: International graduate school of neuroscience

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Title: Hippocampal and perirhinal cortex BOLD responses to familiar and novel odors in awake rats: just a start..

Authors: *C. CHWIESKO[1], B. BOULAT[1], D. WIEDERMANN[2], M. HOEHN[2], M. SAUVAGE[1];
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Abstract: The specific nature of information processing in the hippocampus and the perirhinal cortex, and thus the precise mechanisms by which these structures support cognitive processes like memory is still not well understood. In humans, these questions are most often addressed using functional magnetic resonance imaging (fMRI). This technique has only rarely been used in awake animals, never in the medial temporal lobe in relation to memory function, principally because of the major technical challenges it encompasses. Indeed, animal studies often adopt more invasive approaches, which offer striking advantages on the one hand, but also render results less readily comparable between species. Therefore, investigating memory with fMRI in awake animals and combining it with the advantageous invasive techniques, would address the comparability problem and offer a great potential for the research of hippocampal function in memory. For this reason, we aimed at developing a translational human to animal fMRI compatible cognitive task by adapting a Memory paradigm to awake rats, which requires the recognition of familiar and novel odors. This involved an extensive habituation of the animals as well as the development of new hardware such as a 40 odor- olfactometer, a head fixation system and a new scanning bed, Prior to the experiment, rats underwent a surgery for head fixation and

were thoroughly habituated to the fMRI experimental condition in order to minimize stress levels and maximize attention to the stimuli. During the experiment, a set of familiar and novel odors was presented in a block design to awake rats while hippocampal and perirhinal cortex activity was measured with fMRI. We found for the first time BOLD signals in the rat hippocampus and perirhinal cortex in relation to a fMRI cognitive paradigm in awake rats. The rat hippocampus showed a greater BOLD effect for the familiar odors in contrast to the novel odors, the perirhinal cortex showed the reverse pattern, a greater BOLD effect for the novel odors. The results match well human reports using a similar design. In conclusion, we have successfully adapted a fMRI cognitive paradigm to awake rats, which allows us now to adopt a translational approach with the aim of contributing to solve major debates in memory research by using a combination of fMRI and invasive approaches in awake rats.

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Poster

626. Learning and Memory: Hippocampal Circuits

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Topic: F.02. Animal Cognition and Behavior

Title: Spatiotemporal synaptic input pattern sensitivity of persistent firing in hippocampal CA1 neuron model

Authors: *K. TAKADA[1], K. TATENO[2];
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Abstract: The hippocampus is considered that is basis of construction of the episodic memory. In addition, in a manner that supports the hypothesis, place cells and time cells have been discovered in the hippocampus, the cells that express the space or time. In the receptive field, place cells and time cells show persistent activity. Hippocampal CA1 region is one of the main target of experimental study of place cells and time cells. However, it is difficult to maintain the persistent activity in the network-based in the CA1 region, because of poor recurrent connections. On the other hand, intrinsic persistent firing under cholinergic activation has been discovered in hippocampus. Intrinsic persistent firing potentially supports the activity of place cells and time cells. *In vitro*, intrinsic persistent firing is caused by the perfusion of acetylcholine agonist carbachol and the brief current injection. If the activity of place cells and time cells are

based on intrinsic persistent firing, these need appropriate spatiotemporal pattern of activity of CA3 region that depolarizes CA1 pyramidal cells. In our study, using a network model of hippocampal CA1 and CA3 region, we investigated the spatiotemporal activity patterns of the CA3 network model that leads to the intrinsic persistent firing in the CA1 network model. The present CA1 network model consisted of 100 conductance based pyramidal neuron models and 100 inhibitory interneuron models. The pyramidal neuron model had the calcium-activated non-selective cationic current which is known to underlie intrinsic persistent firing. The stimulation pattern to the CA1 pyramidal neuron models was generated by a Markov chain model. To quantify the input pattern to CA1 pyramidal cells, we used the coefficient of variation (CV) and the local variation (LV) of interspike intervals. In our results, occurrence of intrinsic persistent firing in the CA1 network model was strongly dependent on the LV of input patterns and its duration strongly depended on the CV. Under the low LV condition, spatial coherence of synaptic input to CA1 pyramidal cell models was relatively high. Consequently, intrinsic persistent firing was frequently triggered. In addition, an asymmetric spike timing dependent plasticity rule for the Schaffer collateral synapses reduced the duration of the persistent firing. Our results indicate that, under the poor recurrent connections, the persistent firing of CA1 pyramidal cells are induced by spatially coherent synaptic input generated by the CA3 region. The spatiotemporal activity patterns of the CA3 region may adjust a condition for appearance of place and time cells in the CA1 region.

Disclosures: **K. Takada:** None. **K. Tateno:** None.

Poster

626. Learning and Memory: Hippocampal Circuits

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Topic: F.02. Animal Cognition and Behavior

Support: the Smoking Research Foundation of Japan

Title: The dendrites of granule cell layer neurons are the primary injury sites in the "Brain Diabetes" rat

Authors: ***A. S. SHINGO**[1], R. F. MERVIS[2], T. KANABAYASHI[3], S. KITO[4], T. KOABAYASHI[1], T. MURASE[1];
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Abstract: We previously demonstrated that rats that receive dorsal third ventricle (3V) streptozotocin (STZ) injec- tions (STZ-3V-rats) exhibit cognitive decline as measured by the Morris Water Maze (MWM) and can be used as an animal model of Alzheimer's disease (AD). Immunohistochemical studies of the hippocampal formations of these animals have revealed significant changes in cerebral insulin signalling pathways, as well as marked increases of amyloid beta (Ab) deposition. Here, we performed Sholl analyses of granule cell layer dendrites and measured dendrite spine densities to assess the effect of STZ on hippocampal morphology. In STZ-3V rats as the results, more branching, complex dendrite arborisation, and increased soma size of the granule cells were observed, while spine densities were decreased in all three spine types. An intraventricular injection of a long-acting insulin analogue improved STZ-induced behavioural and immunohistochemical changes. Nevertheless, dendrite spine densities remained diminished, pre- sumably due to overall null changes since new spine formation due to insulin stimulation has been compensated by loss of old spines. It is concluded that cognitive decline in the "Brain Diabetes" rats is primarily due to impaired intracerebral insulin signalling and the ultimate results were injured excitatory inputs through the perforant pathway.

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Poster

626. Learning and Memory: Hippocampal Circuits

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Program#/Poster#: 626.11/AA2

Topic: F.02. Animal Cognition and Behavior

Title: Tau-dependent loss of cell cycle repressors in a mouse model of Alzheimer's disease

Authors: *S. IPPATI;
UNSW, Unsw Sydney, Australia

Abstract: Recent studies reported that a high amount of neurons located in brain regions at risk in Alzheimer's disease, ectopically express proteins related to the cell cycle and proliferation. The re-activation of this process that is normally arrested in mature neurons has been linked to the presence of amyloid-β (Aβ), and the phosphorylation of specific sites of tau. Despite this, the molecular mechanisms that lead to this aberrant cellular process remain poorly understood, and it has not been clarified whether they play a role in the neuronal loss, which characterizes the disease. In the present study, we analyze the elements possibly involved in this molecular process in a transgenic model of Alzheimer's disease. Furthermore, we investigate the direct

effect of Aβ and the involvement of tau on primary hippocampal neurons of mice in the re-activation of the cell cycle. We found that Aβ expression in mice is associated with expression of several cell cycle proteins in neurons surrounding plaques, but more importantly already in the brains of mice before the onset of an overt Aβ pathology. The occurrence of these changes coincides with the onset of memory deficits. Mechanistically, we found that the expression of cell cycle repressors, p27 and p21, was markedly reduced in the brains of APP transgenic mice. This was absent in APP transgenic mice that lack tau expression. Therefore, Aβ may induce cell cycle reentry in neurons by reducing expression of cell cycle repressors in a tau-dependent manner.

Disclosures: S. Ippati: None.

Poster

626. Learning and Memory: Hippocampal Circuits

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Topic: F.02. Animal Cognition and Behavior

Support: Brain Korea 21 PLUS Project for Medical Science, Yonsei University

CABMC (Control of Animal Brain using MEMS Chip) funded by Defense Acquisition Program Administration (UD140069ID)

Title: Neuroprotective effects of placenta-derived mesenchymal stem cell for rat model of dementia

Authors: *J. LEE[1], D. JEONG[1], W. CHANG[2], J. CHANG[1,2];
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[2]Dept. of Neurosurgery, Yonsei Univ. Col. of Med., Seodaemun-gu,Seoul, Korea, Republic of

Abstract: Introductions The neuroprotective effects of mesenchymal stem cell (MSC) in neurodegenerative disease have been recently reported. In contrast of the transplantation effect of MSC derived from bone marrow, adipose tissue and human umbilical cord blood, the study of placenta-derived mesenchymal stem cell (pMSC) is still little known. In this study, we studied the effective method of placenta-derived mesenchymal stem cell (pMSC) transplantation by comparing intracerebroventrical (icv) with intravenous (iv) injection. In addition, we also tried to compare the effect of pMSC transplantation and standard treatment for dementia. Materials and Methods We used the rat model of dementia by damaging basal forebrain cholinergic neurons

using 192 IgG-saporin. 1 week after administration of 192 IgG-saporin, pMSC was injected via intraventricular route (icv, 1.2 x 106cells/8μl) or intravenous route (iv, 5 x 106cells/200μl). And Cyclosporine (immunosuppressant drug) were administrated at peritoneal cavity for preventing immune reaction by innate immunity (daily / 5 weeks). To compare the effect of stem cell therapy and standard therapy, some rats were treated with donepezil and 5 weeks after transplantation, all animals were tested visuo-spatial cognitive functions by Morris water maze. Results The probe test of water maze, performance of pMSC transplantation group and donepezil group increased time spent in target quadrant and in platform zone. Also acetylcholinesterase(AChE) activity was increased in the hippocampus and medial prefrontal cortex(mPFC). Interestingly, iv group showed more improved behavior performance and acetylcholinesterase(AChE) activity than icv group. Immunohistochemistry of stem121 marker of stem cell and iba1 maker of microglia and Western blot of DCX and BDNF were also suggested the beneficial effect of both stem cell therapy and standard donepezil treatment. Conclusions Our result show that pMSC recover spatial memory of dementia model by increasing acetylcholinesterase(AChE) activity. Intravenous injection of pMSC seemed to be more beneficial route for both risk managing and symptom improvement. And pMSC transplantation also showed similar efficacy of the donepezil for improving cognitive function. For determining the superiority of both treatment, further investigation should be needed. Acknowledgements This work was supported (YonseiChallenge) by the Yonsei University Future-leading Research Initiative of 2014 and CABMC (Control of Animal Brain using MEMS Chip) funded by Defense Acquisition Program Administration (UD140069ID).

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Poster

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Neurocure

Gottfried Wilhelm Leibniz Prize

Title: Neuronal responses to conspecifics and social facial touch in the ventral hippocampus

Authors: *R. P. RAO, M. BRECHT;
Humboldt Univ. of Berlin, Berlin, Germany

Abstract: Animals exhibit a range of social interactions (dominance hierarchies, mating and parental behaviours) that rely on their ability to recognize conspecifics. The hippocampus has been demonstrated to be involved in the higher order representation of social signals in humans (Quian Quiroga et al, 2012) and monkeys (Sliwa et al, 2014). However in rodents, the dorsal hippocampus was only weakly modulated by the presence of other rats (von Heimendahl et al, 2012; Zynyuk et al, 2012). This lack of modulation in the dorsal hippocampus could possibly be explained due to the functional segmentation of the hippocampus with the primate anterior hippocampus corresponding to the rodent ventral hippocampus (Moser & Moser, 1998). In our study, we investigate the representation of social signals in the rat ventral hippocampus using a combination of low- and high-speed videography, extracellular neuronal data acquisition and ultrasound recordings. Firing patterns of putative single units were analysed specifically during facial interactions (associated with whisker-to-whisker contacts) in awake, behaving rats while freely interacting with a conspecific across a gap. Social modulation was observed in many ventral hippocampus CA1 stratum pyramidale units (>85%). A large fraction of these (80%) were strongly modulated, with most showing inhibition while a few showed excitatory responses. While some cells responded directly to facial contact, we also observed cells that showed long term modulation of firing that is contingent on the presence of the conspecific. Some cells show individual- and sex-specific responses, and we are currently investigating these aspects of the responses. In summary, the responses in ventral hippocampus appear to be very different from the dorsal hippocampus and also distinct from sensory cortices where firing is seen upon contact (Bobrov et al, 2014). The large fraction of strongly socially modulated neurons implicates the ventral hippocampus in social information processing.

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Poster

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Title: Neurodevelopmental insult by neonatal ventral hippocampal lesion alters periodic activity of dorsal hippocampal neurons in adult rats

Authors: *H.-Y. KAO, A. A. FENTON;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Neonatal ventral hippocampal lesion (NVHL) is a neural excitotoxic lesion that disrupts neurodevelopment. NVHL rats have cognitive deficits and weak hippocampal synchrony of theta and beta oscillations between the two dorsal hippocampi (Lee et al., 2012). Both cognitive ability and the weak synchrony were normalized after NVHL rats received early cognitive training. These observations motivated us to investigate whether NVHL rats have abnormal hippocampal neuronal discharge properties that could be normalized with early cognitive training. Long-Evans male pups were infused with ibotenic acid (NVHL) or ACSF (control) at postnatal day 7. Adult rats were either naïve (control, n = 8; NVHL, n = 8) or tested in the two-frame active place avoidance task (control, n = 6; NVHL, n =3) at postnatal days 56-60. On postnatal days 60-70, spontaneous single unit discharge was recorded from the dorsal hippocampus for 60 min under urethane anesthesia. In some cases, we recorded bilaterally from the hippocampus (control, n = 18; NVHL, n = 16 hippocampus recordings). We first compared the population activity of NVHL and control rats. The spectral power analysis of spiking activity at frequencies from 0 to 12 cycles/hour was calculated. Peaks of activity at any frequency that were greater than two standard deviations from average activity at all frequencies were considered periodic. Six of 16 NVHL, and 3 of 18 control recordings showed periodic spiking activity. Periodicity ranged from 4-5 cycles/hour in NVHL rats, while the periodicity was 6 cycles/hour for control rats. After establishing that the population activity was periodic, we examined single cell activity. In NVHL rats, 24 of 33 (72.7%) cells were periodic and 13 of 24 (54.1%) cells had a periodicity (~4 cycles/hour) similar to the population. For control rats, 17 of 29 (58.6%) cells were periodic and 7 of 17 (41.2%) cells had a periodicity (~6 cycles/hour) similar to the population periodicity. We computed the relationship between single cells and the population by calculating the Person's correlation coefficient (r). The cell-to-population r-values larger than the critical value (0.25) were considered to be significant and were selected from the populations which themselves were periodic. There were 20 of 33 (60%) of cells significantly correlated to the population in NVHL rats and 22 of 29 (76%) in control rats. However, cells from NVHL rats had stronger correlation to the population than cells from control rats. These data indicate that the population dynamics of hippocampal discharge is less stable in NVHL rats. We will determine the effects of early experience on these properties.

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Poster

626. Learning and Memory: Hippocampal Circuits

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SFARI 294388

Canadian Institutes of Health Research

Title: Cognition-sensitive discoordination of local field potentials and place cell spike-field coupling in Fmr1 knockout mice

Authors: *A. A. FENTON[1,3], F. SPARKS[1], Z. TALBOT[2], B. RADWAN[1], D. DVORAK[1,4]; [1]Ctr. for Neural Sci., [2]Sch. of Med., New York Univ., New York, NY; [3]Physiol. & Pharmacol., SUNY, Downstate Med. Ctr., Brooklyn, NY; [4]SUNY Downstate Med. Ctr., Brooklyn, NY

Abstract: Fragile X syndrome (FXS) patients do not express the fragile X mental retardation protein (FMRP). Absence of FMRP causes dysregulated translation, abnormal synaptic plasticity and intellectual disability. But FMRP loss has minimal effects on memory itself, making it difficult to understand why absence of FMRP impairs memory discrimination and exaggerates responses to environmental changes, which is characteristic of FXS patients. While Fmr1 knockout (KO) and wild-type (WT) mice perform cognitive discrimination tasks, we find abnormal coupling between theta and gamma oscillations in distinct perisomatic and dendritic hippocampal CA1 local field potentials of the KO. Perisomatic CA1 theta-gamma phase-amplitude coupling (PAC) decreases with familiarity in both the WT and KO, but activating an invisible shock zone, subsequently changing its location, or turning it off, causes KO but not WT mice to increase PAC at specific dendritic compartments depending on if the cognitive challenge is to learn a new shock location or that shock has turned off. Place cells recorded from WT and Fmr1 KO mice express similar time-averaged firing field properties. But place cell discharge is also organized by a temporal structure that is defined by the phase and frequency of ongoing LFPs at specific perisomatic and dendritic compartments. Thus, on the one hand, we find that the basic electrophysiological properties of individual place cells and frequency band-defined oscillations in the LFP poorly discriminate between WT and Fmr1 KO mice. On the other hand, we find that dynamic patterns of coordinated LFP and related LFP-structured spike-field activity across perisomatic and dendritic CA1 locations are sensitive to the cognitive challenge determined by task demands, as well as cognitive ability expressed as adaptive behavior. This neural coordination provides an electrophysiological basis upon which to differentiate and

mechanistically define the cognitive abilities WT and Fmr1 KO. These findings suggest that hippocampus circuit specific patterns of neural coordination and discoordination provide a pathophysiology that can explain how dysregulated translation leads to intellectual disability in FXS.

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Poster

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Support: NIMH grant R01MH099128

Title: Coordinated slow and fast gamma oscillations predict recollection success and failures in wild-type and Fragile X Syndrome model mice

Authors: *D. DVORAK, B. RADWAN, A. A. FENTON;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Active behaviors are standardly used to assess memory and identify memory deficits in animal models of mental dysfunction, but behavior is only a proxy for the neural events that define cognitive variables like recollection. We identified an electrophysiological signature of memory recollection in the dorsal CA1 hippocampus of mice, while they were not actively moving during a place avoidance task. Although both slow (30-50 Hz) and fast (60-100 Hz) gamma oscillations were decreased before mice initiated avoidance movements, the slow gamma events transiently dominated the fast events about two seconds before successful shock avoidance, but not before failure to avoid shock. These recollection events increased with learning in wild-type as well as Fmr1 mutant mice that model the intellectual disability in Fragile X Syndrome. Wild-type but not mutant mice quickly adapted to relocating the shock zone as well as turning it off. This cognitive flexibility coincided with decreased recollection events in the wild-type but in the mutants the recollection events persisted, consistent with their cognitive inflexibility. Thus recollection is signaled by domination of slow gamma oscillations over fast gamma oscillations in CA1.

Disclosures: D. Dvorak: None. **B. Radwan:** None. **A.A. Fenton:** None.

Poster

626. Learning and Memory: Hippocampal Circuits

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 626.17/AA8

Topic: F.02. Animal Cognition and Behavior

Support: NSF Grant IOS-1146822

Title: Do cortical head-direction cells preserve both directional tuning and temporally-coordinated neural discharge during cognitive control of information in two spatial frames?

Authors: *E. PARK, S. KEELEY, A. A. FENTON;
New York Univ., New York, NY

Abstract: During a two-frame place avoidance task on a rotating arena, spatial information dissociates into a spatial frame of stationary information and a rotating frame of local information. Hippocampus CA1 place cell discharge transiently organizes into same-function groups of coactive cells such that the discharge occurs in temporally-coordinated patterns that switch between representing stationary and rotating locations. We wondered whether other spatially-tuned cells would remain tuned to spatial variables and if so in which spatial frame during the two-frame task. We thus recorded hippocampal place cells and cortical spatially-tuned cells simultaneously while animals performed a one-frame active place avoidance task on a stationary arena and a two-frame task variant on a rotating arena. The notion that spatially-tuned cells (head-direction and grid cells) signal spatial variables for guiding behavior predicts that spatial tuning will be preserved throughout the tasks. Furthermore, notions that the discharge of these cells are governed by strong attractor-like dynamics predicts preserved, coordinated, temporal discharge relationships within the networks of these cells. We find that the fundamental physiological characteristics like the firing rates of directional cells were stable across the stationary and rotating conditions. Despite good spatial cognition performance, directional preference was lost in the rotating condition. In contrast, the temporal organization of discharge was preserved. Estimates by correlating pairs of spike trains showed preserved pair-wise correlations across the stable and rotating conditions. These findings are support for the notion that directional cells are organized by attractor dynamics and those responses to azimuthal inertial direction is secondary to these network dynamics.

Disclosures: **E. Park:** None. **S. Keeley:** None. **A.A. Fenton:** None.

Poster

626. Learning and Memory: Hippocampal Circuits

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 626.18/AA9

Topic: F.02. Animal Cognition and Behavior

Support: R01MH084038

Title: Hyperactivity, short- and long-term memory impairments during otherwise intact cognitive control in the gestational day 17 methylazoxymethanol acetate (MAM) rat model of neurodevelopmental insult

Authors: *K. C. O'REILLY, A. A. FENTON;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Like diverse forms of mental illness, schizophrenia is increasingly considered to have a neurodevelopmental origin. *In utero* exposure to the mitotoxin methylazoxymethanol acetate (MAM) at gestational day 17 results in altered hippocampus morphology and function and impaired spatial memory in rats. Because cognitive impairments are the most debilitating for schizophrenia patients, we asked if MAM rats displayed cognitive deficits during adolescence (36/37 days old), when symptoms of schizophrenia first emerge, or during adulthood (60-70 days old). We assessed cognitive control, short- and long-term memory, and locomotor behavior, using the hippocampus-dependent two-frame active place avoidance task, during which rats avoid a stationary shock zone on a rotating arena. The rats were tested over two days (eight 10 min trials/day). We measured locomotor activity (distance actively moved), ability to learn (learning curve over 16 trials), short-term memory (entrance latency, time to the first error for each trial), and long-term memory (entrance latency on the first trial of the second day). Adolescent and adult MAM rats were hyperactive during all trials. Both adolescent and adult MAM rats made significantly more errors than controls on the first day of testing. However, normalizing the errors by locomotor activity (errors/m), revealed that MAM rats were not different from control rats. Additionally, the learning curves of MAM rats, which could be described by exponential decay, were not different from controls. MAM rats showed impaired short-term memory: in contrast to control rats, MAM rats did not increase their entrance latency by the end of the first day. Hyperactivity is unlikely to account for shorter entrance latencies because the rats remained hyperactive on the second day of testing, but their entrance latencies increased to the same levels as controls. The distance walked prior to the first error was shorter in adolescent and adult MAM rats, which further confirmed that hyperactivity did not account for the short entrance latency. During all trials, adolescent and adult MAM rats were able to avoid the shock zone for the same maximum time as control rats, indicating that within trial

memory was not impaired. Adolescent and adult MAM rats have impaired long-term memory, indicated by shorter latency to enter and shorter entrance distance on the first trial of day two. We conclude that adolescent and adult MAM rats are hyperactive and have impaired short-term and long-term memory. Because MAM rats are able to learn the shock zone and do not make more errors when hyperactivity is accounted for, we conclude that there is no evidence of impaired cognitive control.

Disclosures: K.C. O'Reilly: None. **A.A. Fenton:** None.

Poster

626. Learning and Memory: Hippocampal Circuits

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Program#/Poster#: 626.19/AA10

Topic: F.02. Animal Cognition and Behavior

Support: SFARI 294388

CIHR

NIH MH96331-5

Title: Neural discoordination within the hippocampus place cell network during cognitive control in the Fragile X mouse model of Autism Spectrum Disorder

Authors: *F. T. SPARKS[1], Z. N. TALBOT[2], D. DVORAK[3], A. A. FENTON[1];
[1]Ctr. for Neural Sci., New York Univ., New York, NY; [2]New York Univ. Sch. of Med., New York, NY; [3]SUNY Downstate Med. Ctr., Brooklyn, NY

Abstract: The hippocampus (HPC) is the model neural system facilitating high-order cognitive functions such as autobiographical memory, spatial navigation, and cognitive control. Though much focus has been placed on dedicated spatial tuning properties of individual place cells, the HPC also exhibits dynamic functional grouping of place cells that are temporally organized such that subpopulations collectively participate in representing information. We hypothesize that abnormalities in neural coordination underlie dysfunctional cognitive control, the ability to selectively use relevant information while ignoring distraction. Cognitive control deficits are a core feature of Fragile X syndrome (FXS) the most common form of intellectual disability and a syndromic form of Autism Spectrum Disorder (ASD). Assessment of this hypothesis was performed using a Fragile X mutant mouse model (Fmr1-KO) that lacks the Fmr1 gene. Mice performed two-frame active place avoidance tasks to evaluate cognitive control. To assess neural

coordination, we characterized first-order features of individual place cells, and then analyzed higher-order features of place cell ensemble dynamics. Place cells were recorded concurrently with local field potentials from dorsal CA1 region of HPC in Fmr1-KO and wild-type (WT) mice. During pre-training with no shock on the stationary arena, individual Fmr1-KO place cells formed normal place fields compared to WT place cell properties such as inter-spike interval, firing rate map coherence, number of place fields, and field size. During slow continuous rotation of the arena, place cells in both genotypes maintained place fields anchored to distal cues. Ensemble coordination was estimated by Kendall's correlation (tau) across short time scales in pairs of place cell spike trains. Arena rotation had minimal effect on tau calculated up to 1 sec. Analysis of place cell spike trains prior to and following active place avoidance training revealed differences in coordinated ensemble activity across genotype. Following active place avoidance, the number of significant discordant cell pairs is silenced in the KO on various time scales < 1sec, whereas WT maintains proportion of discordant pairs. Overdispersion, a measure of within-field firing variability is significantly increased in the Fmr1-KO but only following task training. Together, these results illustrate normal properties of individual place fields in Fmr1-KO mice and abnormal neural coordination within the Fmr1-KO place cell network during cognitive control, supporting the hypothesis that abnormal neural coordination contributes to cognitive control deficits found in FXS and ASD.

Disclosures: **F.T. Sparks:** None. **Z.N. Talbot:** None. **D. Dvorak:** None. **A.A. Fenton:** None.

Poster

626. Learning and Memory: Hippocampal Circuits

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Program#/Poster#: 626.20/AA11

Topic: F.02. Animal Cognition and Behavior

Support: MH081060

Title: Characterization of the postnatal loss of mef2c selectively in the brain

Authors: ***M. MAHGOUB**[1], M. ADACHI[2], P.-Y. LIN[1], L. M. MONTEGGIA[1];
[1]Dept. of Neurosci., UTSW Med. Ctr. At Dallas, Dallas, TX; [2]Astellas, Chicago, IL

Abstract: Myocyte enhancer factor 2 (MEF2) transcription factors are crucial for cell differentiation and development in peripheral tissues as well as in brain. In the mammalian genome the MEF2 family is comprised of 4 genes that share high homology with the family of MAD (MCM1-Agamous-Deficiens-Serum response factor) box transcription factors. The Mef2c

gene member of the family is expressed the earliest in embryonic brain development and maintains high levels of expression in adult brain including the cortex, striatum and hippocampus, particularly the dentate gyrus subregion, suggesting potential roles in adult brain function. In previous work we had generated conditional Mef2c knockout mice in which Mef2c was deleted embryonically selectively in brain and observed an increase in the number and function of synapses that was accompanied by deficits in learning and memory. However, the embryonic deletion of Mef2c could result in compensation effects that impact the resulting phenotypes. Therefore, in this study we generated conditional Mef2c knockout mice using the calcium/calmodulin-dependent protein kinase II (CaMKII)-Cre93 driver line that targets broad forebrain regions including hippocampus to examine whether the postnatal deletion of Mef2c impacts behavior and synaptic plasticity. We find that postnatal deletion of Mef2c in the brain results in a significant increase in spine numbers. Data will be presented on the behavioral and synaptic characterization of these conditional knockout mice to examine the role of endogenous Mef2c expression in CNS function.

Disclosures: **M. Mahgoub:** None. **M. Adachi:** None. **P. Lin:** None. **L.M. Monteggia:** None.

Poster

626. Learning and Memory: Hippocampal Circuits

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 626.21/AA12

Topic: F.02. Animal Cognition and Behavior

Title: Spatial representation of place cells of APPswe/PSEN1dE9 Alzheimer's mouse model

Authors: *M.-J. PARK[1,2], H. RHIM[1,2], J. CHO[1,2];
[1]Korea Inst. of Sci. and Technol., SEOUL, Korea, Republic of; [2]Korea Univ. of Sci. and Technol., Daejeon, Korea, Republic of

Abstract: The hippocampus plays an important role in spatial learning and memory and also is known to be susceptible to neurodegenerative disorder, such as Alzheimer's disease (AD). APP/PS1 transgenic mice model is used to mimic the pathological and physiological impairments in AD. Our previous study has shown that APP/PS1 mice (at 10-12 months of age) were impaired hippocampal dependent learning and memory in Morris water maze and passive avoidance test. Although hippocampal dependent memory impairments in AD have been well studied, much less is known about neurophysiological mechanism related to memory deficits in AD. The hippocampal place cells are believed to be a neural substrate for spatial memory and encode the animal's location in a given environment. Here, to examine the function of

hippocampal neurophysiology in AD, we conducted a hippocampal dependent place recognition memory test and CA1 & CA3 place cell recordings using APP/PS1mice (at 10-12 months of age). APP/PS1 mice showed impaired place recognition memory performance compared to WT mice by showing no preference to the object that has been moved to a new location. In addition, both CA1 and CA3 place cells recorded in APP/PS1mice showed decreased place cell stability in a familiar environment, which accompanied with decreased spatial coherence and decreased selectivity of place field. Furthermore, ratio of intra-burst spikes to total spikes and mean inter and intra-burst intervals were significantly altered, whereas mean firing rates were not altered in both CA1 and CA3 place cells in APP/PS1 mice. These results suggest that reduced place cell stability and altered physical properties of spiking in both CA1 and CA3 place cells may provide the neuronal basis underlying the impaired hippocampal dependent learning and memory in AD.

Disclosures: **M. Park:** None. **H. Rhim:** None. **J. Cho:** None.

Poster

626. Learning and Memory: Hippocampal Circuits

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Program#/Poster#: 626.22/AA13

Topic: F.02. Animal Cognition and Behavior

Title: Learning and memory induced CA1 activity *in vivo* and its deficiency in a mouse model of Alzheimer's disease

Authors: *S. POLL, L. C. SCHMID, J. STEFFEN, D. EHNINGER, M. FUHRMANN; German Ctr. for Neurodegenerative Dis. (DZNE), Bonn, Germany

Abstract: The hippocampus is critically involved in learning and memory processes and one of the first regions affected in Alzheimer’s disease (AD). Pyramidal neurons of the hippocampal CA1 region substantially contribute to memory acquisition and retrieval of recent and remote memories. Memory retrieval in part involves the same neuronal ensemble that is active during acquisition - a process called reactivation of a memory trace. We asked whether memory trace formation was altered in a mouse model of AD. For this purpose we performed repetitive *in vivo* two-photon imaging of individual hippocampal CA1 pyramidal neurons combined with contextual fear conditioning. Neuronal activity was monitored by tracing expression of the immediate early gene c-fos in a transgenic FosGFP mouse. The mouse model was crossbred to APP/PS1 transgenic mice that served as a model for AD. We revealed a major fraction of continuously fosGFP expressing cells indicating a regularly active subset of CA1 pyramidal neurons. A minor but specific neuronal ensemble was identified to be active after fear

conditioning and reactivated during memory retrieval potentially representing a memory trace. This learning- and memory-specific change of neuronal activity was absent in the mouse model of AD. Our data suggest that aberrant learning-dependent activity of pyramidal CA1 neurons contributes to contextual memory impairments in APP/PS1 mice and potentially in AD.

Disclosures: S. Poll: None. **L.C. Schmid:** None. **J. Steffen:** None. **D. Ehninger:** None. **M. Fuhrmann:** None.

Poster

626. Learning and Memory: Hippocampal Circuits

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Topic: F.02. Animal Cognition and Behavior

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ORIP/OD P51OD011132 (formerly NCRR P51RR000165)

Title: Hippocampal inactivation impairs object-in-place associations and delay-dependent recognition in rhesus monkeys

Authors: *A. R. WEISS, J. BACHEVALIER, M. C. ALVARADO;
Emory University/YNPRC, Atlanta, GA

Abstract: The present study compared the effects of transient hippocampal inactivation on delay-dependent recognition memory and spatial relational memory, as measured by the visual paired-comparison paradigm (VPC), a task known to be impacted by permanent hippocampal lesions (Nemanic et al., 2004, *J. Neuroscience*, *24*; Bachevalier & Nemanic, 2008, *Hippocampus, 18*). Using modified techniques developed by Malkova and colleagues (Forcelli et al., 2014, *PNAS, 111*), we infused either 2-4µl muscimol, a GABA-A agonist (1µg/1µl) or the same volumes of vehicle (saline), or no infusion into the hippocampi of two awake, behaving, adult monkeys (M1 and M2). For each subject, the infusion targeted one anterior and one posterior coordinates of the hippocampus in each hemisphere, allowing for three inactivation Conditions: A) anterior + posterior; B) anterior only; C) posterior only. Monkeys were tested using two versions of the VPC paradigm: 1) Object-in-Place, in which the comparison is

between a 5-object array and the same 5-object array but with the spatial positions of 3 of the objects rearranged; a short 5s delay was used; or 2) Object-Replace, in which the comparison is between a 5-object array and the same array with 3 of the objects replaced with novel ones; short (5s) and long (60s) delays were used. Here, we report preliminary results from Condition A (combined infusion in anterior and posterior regions). Object-in-Place: For M1, bilateral infusions of muscimol, but not saline or no infusion, reliably lowered its novelty preference to chance levels (test-value=50%) [muscimol: $t(21)=0.87$, $p=0.395$; saline: $t(35)=2.66$, $p=0.012$; No infusion: $t(39) = 2.80$, $p = .008$]. Object-Replace: for M2, muscimol injections decreased its novelty preference scores to chance levels at the long delay [muscimol: $t(9)=0.71$, $p=0.46$; saline: $t(8)=3.20$, $p=0.01$; No infusion: $t(23) = 4.88$, $p < .001$; drug effects ANOVA [$F(2,40) = 3.30$, $p < .05$], but not at the short delay [all $p > .05$; drug effects ANOVA $F(2,43) = 0.26$, ns]. These preliminary results suggest that hippocampal inactivation alters object recognition memory at long delays as well as spatial relational memory even at a brief delay. These impairments were similar to those observed after excitotoxic hippocampal lesions in adult monkeys. Future inactivations of hippocampal anterior vs posterior portions may help refine our understanding of its role in support of memory.

Disclosures: A.R. Weiss: None. **J. Bachevalier:** None. **M.C. Alvarado:** None.

Poster

626. Learning and Memory: Hippocampal Circuits

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 626.24/AA15

Topic: F.02. Animal Cognition and Behavior

Title: Morphological analysis of CA1-CA3 neurons of dorsal hippocampus and evaluating the learning and spatial memory process in adult Taiep rats

Authors: F. MEDINA[1], *A. B. SILVA[2];
[1]Escuela de Biologia, [2]Benemérita Univ. Autónoma de Puebla, Puebla, Mexico

Abstract: The *Taiep* rat characterized by tremor, ataxia, immobility episodes, audiogenic epilepsy and hinlimb paralysis, is an autosomic recessive myelin mutant in which hypomyelination and progressive demylination of the central nervous system (CNS) is present during development, resulting in numerous molecular, morphological and functional abnormalities of the neurons. The aim of this study was determine the morphological characteristics of the CA1-CA3 of pyramidal neurons of dorsal hippocampus and the performance of learning and spatial memory process in adult *Taiep* rats. Forty-eight male adult

rats Sprague Dawley (SD) were used, they were divided in two lots of twenty-four rats each one, these in turn were divided in three groups: 1) *Taiep,* 2) carries and 3) SD (n=8). One lot was used for the morphological analysis and the second lot was used for the object recognition task (OR). For the dendritic morphological characteristics, coronal cuts of dorsal hippocampus were studied using the Golgi-Cox staining technique followed with Sholl analysis. The OR task evaluates the spatial memory in rats, based on the time of exploration of familiar and novel objects. In the first trail (T1), the rat explored four objects (familiar objects) during five minutes, after a delay of five minutes, the second trail (T2) was performed, three objects used in T1 and a novel object was used; all the objects were changed of position. We evaluated the time of exploration for the objects in T1 and T2, when the rats explore the novel object for a greater time period, suggest memory for the familiar object, or when they explore the novel and familiar objects indistinctly, suggest a lack of recall or loss of memory for the familiar objects. As a result we observed that the carried rats showed a decrease in the concentric circles 14-21 of the apical dendritic arborization of CA3 neurons and a diminution in the concentric circles 11-13 and 15 of basal dendritic arborization in CA3 neurons of *Taiep* rats. For the dendritic length for order of branching, the *Taiep* rat showed a diminution of the dendritic length of fourth order (basal branch) and first order (apical branch) of CA1 neurons and a diminution in third order (basal branch) in CA3 neurons. The results obtained in the OR task, there were not significant differences between the groups. Due to the myelinic alterations presents in the *Taiep* rat in the CNS, the severity of symptoms presenting in adulthood and the alterations in the dendritic arborization of dorsal hippocampus, the learning and memory task were performed efficiently.

Disclosures: F. Medina: None. **A.B. Silva:** None.

Poster

626. Learning and Memory: Hippocampal Circuits

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Topic: F.02. Animal Cognition and Behavior

Support: EU FP7 grant SpaceCog

The Wellcome Trust

Title: A computational model of the ‘what’ and ‘where’ of episodic memory

Authors: *A. BICANSKI, N. BURGESS;
Inst. of Cognitive Neurosci., London, United Kingdom

Abstract: The Byrne, Becker and Burgess (Psych Rev, 2007; 'BBB') model of spatial memory provides a plausible account of high-level, cognitive phenomena such as imagery and neglect, at the level of the responses of individual neurons. In the model, allocentric spatial representations consisting of place cells, boundary vector cells and perirhinal texture/identity neurons, are stored as attractors in the medial temporal lobe (MTL). These representations are translated to/from corresponding egocentric representations in parietal areas, via an intermediate 'gain field' circuit, thought to reside in retrosplenial cortex. We present an updated version of the BBB-model, extended in two ways. First, we include an agent model, allowing the network to be driven by the current perceptual input, allowing for sensory driven self-localization (as opposed to pattern completion in the MTL). Second, we incorporate representations of discrete objects into the egocentric parietal and the allocentric medial temporal representations. Previously the BBB-model was only capable of representing extended topographical features (e.g., buildings), via boundary vector cells. We propose that this geometrical representation can be furnished with content (i.e. discrete objects) via place cells (firing in response to a given object in a given location) and object-specific cells akin to boundary vector cells (see e.g., landmark-vector cells, Deshmukh et al. 2013; object trace cells, Tsao et al. 2013). Crucially these object representations can be encoded on the fly (as the agent explores the environment) and updated (e.g. after displacement) without affecting the transformation between reference frames. The model can also recall the locations of objects by re-instantiating a view of them in imagery and retrieving the place linked to the object in the pattern-completing MTL network. Finally, embedding object information into the MTL representations for spatial memory allows us to explore the item-context dichotomy in a mechanistic, neural-level model of memory and imagery. Byrne, P., Becker, S., & Burgess, N. (2007). Remembering the past and imagining the future: a neural model of spatial memory and imagery. Psychological review, 114(2), 340. Deshmukh, S. S., & Knierim, J. J. (2013). Influence of local objects on hippocampal representations: landmark vectors and memory. Hippocampus, 23(4), 253-267. Tsao, A., Moser, M. B., & Moser, E. I. (2013). Traces of experience in the lateral entorhinal cortex. Current Biology, 23(5), 399-405.

Disclosures: **A. Bicanski:** None. **N. Burgess:** None.

Poster

626. Learning and Memory: Hippocampal Circuits

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Topic: F.02. Animal Cognition and Behavior

Support: DFG Grant FOR1581

Title: Learning-related single-neuron activity changes in the nidopallium caudolaterale and hippocampus

Authors: *S. STAROSTA[1], O. GUNTURKUN[1], M. C. STÜTTGEN[2];
[1]Ruhr Univ., Bochum, Germany; [2]Univ. Med. Ctr. Mainz, Inst. of Pathophysiology & Focus Program Translational Neurosci., Mainz, Germany

Abstract: Adapting behavior to changing circumstances frequently entails both the acquisition and the extinction of conditioned responding. While acquisition is intuitively regarded as learning, the reduction of responding is often seen as a behavioral signature of forgetting. However, decades of research show that the reduction in responding following the repeated omission of an expected reinforcement (extinction) is far better described as a consequence of a second inhibitory learning process. Studies employing Pavlovian fear conditioning in rodents identified the hippocampus as well as the prefrontal cortex as two key players involved in the acquisition and extinction of a fear response. By contrast, the involvement of these structures in the acquisition and extinction of appetitive, operantly conditioned responses is not well characterized. To investigate the time course of neuronal plasticity during acquisition, extinction, and reacquisition in an operant conditioning paradigm with positive reinforcement, we established a behavioral paradigm enabling us to monitor single-neuron activity across these learning stages in a single experimental session lasting >1,000 trials. We subjected pigeons to a visual discrimination task with two stimulus pairs. One pair was familiar to the animals; thus, they knew how to respond to these stimuli. This condition served as a control. The other pair of stimuli consisted of pictures which the animals had never seen before. Thus, in each behavioral session, animals had to learn how to respond to either of two stimuli. After reaching a pre-defined performance criterion, responding to one of the novel stimuli was no longer reinforced. Once responding to this stimulus had decreased (i.e., had been extinguished), the response was reinforced again, leading to its reacquisition. While animals were performing this task, we recorded the activity of single neurons in two regions of the avian brain: nidopallium caudolaterale (an associative forebrain structure thought to be functionally analogous to mammalian prefrontal cortex); hippocampus (the avian homolog to mammalian hippocampus). The observed highly dynamic response patterns during learning are discussed in regard to similarities and differences between learning processes, brain regions, and species.

Disclosures: **S. Starosta:** None. **O. Gunturkun:** None. **M.C. Stüttgen:** None.

Poster

626. Learning and Memory: Hippocampal Circuits

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Topic: F.02. Animal Cognition and Behavior

Support: Intramural Research Program of NIDA/NIH

Title: Mesopontine median raphe regulates hippocampal ripple oscillation and memory consolidation

Authors: *D. V. WANG, S. IKEMOTO;
NIH, Baltimore, MD

Abstract: Memory consolidation integrates newly acquired information into preexisting neural network without confusing it with old memories. To accomplish this, a precise regulation of the consolidation process is essential. Converging evidence suggests that sharp wave-associated field oscillations (~200 Hz) of the hippocampus, referred to as ripples, are important for consolidation of explicit memory. We have recently shown that the mesopontine median raphe (MnR) plays an important role in regulating hippocampal ripple activity and memory consolidation. In particular, when a group of MnR neurons (type I) was active, ripples were absent. These neurons display tonic and burst activity in pacing ripple activity. We also found that these type I neurons were not serotonergic or GABAergic using electrophysiological recording combined with optogenetics in transgenic mice (known as 'phototagging'). To test the hypothesis that type I neurons are glutamatergic, we performed phototagging of VGlut3-positive MnR neurons. Preliminary results showed that MnR type I neurons, identified by its correlation with hippocampal ripple activity, responded to photostimulation with short latency (5 ms or less), confirming that they are VGlut3-positive. We are currently examining how photoactivation and photoinhibition of the MnR VGlut3-positive neuron would affect hippocampal ripple activity and memory consolidation processes. We are also examining how MnR neurons regulate ensemble of hippocampal place cells, using the *in vivo* calcium imaging technique

Disclosures: D.V. Wang: None. **S. Ikemoto:** None.

Poster

626. Learning and Memory: Hippocampal Circuits

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Topic: F.02. Animal Cognition and Behavior

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Evelyn F. McKnight Brain Research Foundation

Title: Upregulation of estrogen receptor alpha restores spatial memory and NMDA receptor synaptic function

Authors: *L. A. BEAN[1], A. KUMAR[2], A. RANI[2], M. GUIDI[3], P. CRUZ[2], T. C. FOSTER[2]; [1]Neurosci., [2]Univ. of Florida, Gainesville, FL; [3]Noldus Information Technol., Leesburg, VA

Abstract: The decline in the therapeutic effects of estradiol (E2) on cognition during aging is thought to result from a loss of neural plasticity due to altered expression of estrogen receptors. We tested the hypothesis that upregulating hippocampal expression of estrogen receptor alpha (ERα) or estrogen receptor beta (ERβ) would restore the therapeutic potential of E2 treatment on cognition and rejuvenate E2 induced hippocampal plasticity in aged animals that experienced prolonged hormone deprivation. We employed adeno-associated viral (AAV) vectors to enhance expression of ERα, ERβ, or green fluorescent protein (GFP) in the CA1 region of dorsal hippocampi of female Fisher 344 rats (18.5 months.) whose ovaries had been removed 14 weeks earlier. One week after virus injections, animals were treated for five weeks with cyclic injections of 17β-estradiol-3-benzoate (EB, 10 μg) or oil (GFP+EB: n=13, GFP+Oil: n=12, ERβ+EB: n=11, ERβ+Oil: n=11, ERα+EB: n=13, ERα+Oil: n=12). Spatial water maze performance was examined forty-eight hours following EB/oil treatment. EB failed to improve cognition in GFP animals, consistent with the idea that long-term hormone deprivation in older animals is associated with closing of the E2 therapeutic window. Increased expression of ERβ was associated with a modest learning impairment, regardless of treatment. In contrast to GFP and ERβ groups, spatial memory was enhanced in animals that express ERα and received EB treatment indicating ERα expression reinstated E2 responsiveness. This idea was supported by examination of hippocampal synaptic transmission. EB treatment had no effect on N-methyl-D-aspartate (NMDA) receptor synaptic transmission in the GFP group confirming a decrease in hippocampal EB responsiveness with prolonged E2 deprivation. Enhanced NMDA receptor synaptic transmission was observed in animals expressing ERα and treated with EB compared to GFP animals treated with EB or ERα animals treated with oil. This is the first demonstration that the E2 therapeutic window and hippocampal responsiveness can be reinstated by enhanced expression of estrogen receptors, specifically ERα.

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Poster

626. Learning and Memory: Hippocampal Circuits

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New Jersey Governor 's Council for Medical Research and Treatment of Autism

JSPS Postdoctoral Fellowships

CREST-JST

Title: Genetic activation of stathmin impairs adult hippocampal neurogenesis, spinogenesis, and NMDA receptor-dependent memory

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Abstract: Activation of postsynaptic NMDARs triggers complex downstream signaling events, including cAMP-response-element binding protein (CREB)-dependent gene transcription, which is critical for memory in many species. To exert their physiological roles, NMDARs must be transported into dendrites and synaptic sites. Thus, dendritic transport of NMDARs along microtubules is a prerequisite for NMDAR activity. However, little is known about the mechanisms underlying microtubule-based dendritic transport of NMDARs. Among microtubule-associated proteins, stathmin, a negative regulator of microtubule formation, is highly expressed in certain regions of the adult mammalian brain, including the dentate gyrus (DG) of hippocampus. In this study, we examined the role of the DG stathmin in neurogenesis, dendritic development, and NMDAR-dependent memory formation. To this end, we employed transgenic mice expressing the unphosphorylatable constitutively-active stathmin4A (Stat4A) protein in the tetracycline-dependent manner in the DG of hippocampus. Expression of Stat4A led to impaired adult hippocampal neurogenesis and aberrant maturation of the DG granule neurons. It was associated with deficient intracellular transport of the NMDAR subunits GluN2A and GluN2B and a decrease in CREB-mediated gene transcription known to be dependent on NMDAR function. Consistent with the NMDAR signaling deficit, transgenic mice expressing Stat4A showed deficient NMDAR-dependent memory in contextual discrimination learning, which is also dependent on neurogenesis. In contrast, Stat4A mice had normal NMDA receptor-independent memory tested by contextual fear conditioning with upstairs/downstairs protocol. The deficits in neurogenesis and NMDA receptor-dependent memory in Stat4A mice were

reversed by suppression of transgene expression with doxycycline (dox). These results indicate a crucial role for stathmin in the DG maturation and hippocampus-dependent memory formation. Our results demonstrate the role of stathmin in controlling intracellular transport of NMDA receptors, neurogenesis, neuronal maturation, and contextual discrimination.

Disclosures: S. Uchida: None. **I. Chévere-Torres:** None. **C. Hevi:** None. **Y. Watanabe:** None. **G.P. Shumyatsky:** None.

Poster

627. Learning and Memory: Gamma and Theta Activity

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CFI Leaders Opportunity Fund (25026)

Title: Enhancing prefrontal neuron excitability enables the associative learning over an extended temporal delay

Authors: *X. YU[1], J. VOLLE[2], H. SUN[2], S. E. TANNINEN[2], N. INSEL[2], K. TAKEHARA-NISHIUCHI[1,2];
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Abstract: The medial prefrontal cortex (mPFC) has been implicated in cognitive processes that involve the linking of multiple stimuli over temporal delays. When animals learn to associate a neutral conditioned stimulus (CS) with an aversive eyelid shock (US) in trace eyeblink conditioning, the mPFC exhibits several characteristic activity patterns during the CS-US interval, including increased amplitude of theta oscillations (Takehara-Nishiuchi et al., 2011) and persistent single neuron firing (Takehara-Nishiuchi and McNaughton, 2008). These neuron activity patterns indicate the sustained activation of mPFC network during the temporal delay; however, its causal relation to the proposed linking function remains unknown. Here, we artificially elevated neuron excitability in the mPFC and examined its effect on stimulus-evoked oscillatory activity and memory formation in trace eyeblink conditioning. Neuron excitability was manipulated by using a pharmacogenetic approach, in which either the evolved human M3-muscarinic receptor (hM3Dq rats) or, as a control, green fluorescent protein (GFP rats) was expressed, through viral transduction, in mPFC pyramidal neurons of adult rats. The hM3Dq-

expressing neurons were activated by systemic injection of the hM3Dq ligand, clozapine-N-oxide (CNO, 0.1 mg/kg body weight). All rats received a modified version of trace eyeblink conditioning with an extended CS-US interval (750 msec), during which local field potentials (LFPs) were recorded in the prelimbic region of mPFC. Each group was split into two sub-groups which received either CNO or saline thirty minutes before daily conditioning started. We found that while the majority of control rats could not acquire the CS-US association (15 non-learners/ 20 rats in the hM3Dq-saline, GFP-saline, and GFP-CNO groups), most rats with the enhanced prefrontal neuron excitability were able to acquire the association (11 learners/13 rats in the hM3Dq-CNO group). Moreover, LFP activity was elevated upon the CS presentation in all groups. After the offset of CS, the amplitude of theta (4-12 Hz), beta (12-30 Hz) and gamma (30-80 Hz) oscillations stayed high toward the US onset in the hM3Dq-CNO group and the learners in the control groups whereas in the non-learner controls it immediately dropped to a baseline level. Our results suggest that the enhancement of prefrontal neuron excitability is sufficient to extend the stimulus-induced activation of the mPFC network, which contributes to the linking of stimuli separated by a temporal delay.

Disclosures: **X. Yu:** None. **J. Volle:** None. **H. Sun:** None. **S.E. Tanninen:** None. **N. Insel:** None. **K. Takehara-Nishiuchi:** None.

Poster

627. Learning and Memory: Gamma and Theta Activity

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Topic: F.02. Animal Cognition and Behavior

Support: Univeristy of Aberdeen

SULSA

Title: Parvalbumin cells in prefrontal cortex support working memory by modulating theta and gamma power

Authors: ***M. U. WOLOSZYNOWSKA-FRASER**[1], B. CROUCH[1], B. PLATT[1], P. WULFF[2], G. RIEDEL[1];
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Abstract: The inhibitory circuitry of the prefrontal cortex (PFC) is involved in working memory and modulation of brain oscillations. Alterations in this network, and especially GABAergic cells

that express calcium-binging protein parvalbumin (PV), are thought to determine some of the cognitive deficits observed in schizophrenia. To assess the involvement of PV+ interneurons in PFC-dependent behaviours, we selectively inactivated PV-cells in prelimbic and infralimbic PFC via virus-mediated expression of tetanus toxin light chain (TeLC). We found that functional removal of PV+ neurons leads to specific impairments in working memory and cognitive flexibility, and these represent the main cognitive domains affected in schizophrenia. PV-TeLC mice displayed Y-maze alternation index reduction of ~10% ($p<0.04$), while the number of arm entries was not different. For physiological recordings, the Y-maze was redrawn and each arm divided into two equal-sized zones - proximal (close to the central decision point) and distal (far end). Zone entry was event-mapped onto continues local field potential recordings from infra-limbic PFC and CA1. Globally, there was lower hippocampal power in theta band frequencies ($p<0.05$ for 6.5-9 Hz) and reduced PFC gamma power in distal and proximal (decision) zones in PV-TeLC mice ($p<0.05$). While controls showed heightened hippocampal power in the gamma range when in the proximal zone close to the decision point relative to the distal zone of each arm ($p<0.05$), PV-TeLC mice did not. This suggests that the PV-TeLC animals are unable to modulate neuronal activity depending on the cognitive demand. However, PV-TeLC mice showed normal anxiety (light/dark box) or anhedonia (sucrose preference test) phenotypes. These results show that prefrontal PV+ interneurons control task-relevant neuronal activity in different brain regions engaged with working memory such as hippocampus. Similar signalling anomalies may thus underlie cognitive deficits found in schizophrenia.

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Poster

627. Learning and Memory: Gamma and Theta Activity

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Topic: F.02. Animal Cognition and Behavior

Support: CNPq

CAPES

FAPERN

Title: A respiration-coupled rhythm in the rat hippocampus independent of theta and cortical slow oscillations

Authors: *A. B. TORT, A. L. V. LOCKMANN, R. N. LEÃO, D. A. LAPLAGNE;
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Abstract: During slow-wave sleep and deep anesthesia, the rat hippocampus displays a slow oscillation (SO; <1.5 Hz) that follows up-and-down state transitions in the neocortex (Wolansky et al, 2006). There has been some debate as to whether this local field potential (LFP) rhythm is entrained by respiratory inputs (Lockmann and Belchior, 2014). For instance, in ketamine-anesthetized rats, Fontanini et al. (2003) reported oscillations of similar frequency in the piriform cortex of rats, which were locked to the respiratory cycle. However, Vizcko et al. (2014) convincingly demonstrated that hippocampal and neocortical SO recorded from rats during either urethane or ketamine anesthesia, as well as during natural slow-wave sleep, were not coupled to respiration. In the mouse hippocampus, however, Yanovsky et al. (2014) have recently described a slow oscillation entrained by nasal respiration under urethane anesthesia; this rhythm, dubbed hippocampal-respiration rhythm (HRR), was most prominent in the dentate gyrus, and could be distinguished from simultaneously occurring theta waves (Yanovsky et al., 2014). Therefore, whether slow frequency oscillations in the rat hippocampus couple to respiration or not is at issue. Here we have concomitantly recorded respiration activity along with hippocampal, neocortical and olfactory bulb (OB) LFPs in rats anesthetized with urethane. During the course of anesthesia, time-resolved spectral analyses showed that hippocampal LFPs transitioned between activity states characterized by the emergence of different oscillations. By jointly analyzing multisite LFP recordings and respiratory cycles, we could distinguish 3 types of oscillatory activity: SO, HRR and theta. Moreover, we could find time periods in which all three oscillations co-existed. While theta oscillations tended to be faster (>3 Hz) than HRR and SO, these latter two were typically of similar peak frequency (~1 Hz). Our results therefore solve the apparent contradictions among previous studies (Fontanini et al., 2003; Vizcko et al., 2014; Yanovsky et al., 2014) by demonstrating that the rat hippocampus can produce two types of slow oscillations <1.5 Hz: one that is entrained to the respiration cycle (HRR), and another that phase-locks to neocortical up-and-down transitions (SO). In all, the results suggest caution when referring to "slow oscillations" in the rodent hippocampus, as there may be different oscillatory activities that can overlap in time of occurrence as well as in peak frequency. Since they synchronize with different brain circuits, however, we postulate that each activity pattern plays unique roles in information processing.

Disclosures: **A.B. Tort:** None. **A.L.V. Lockmann:** None. **R.N. Leão:** None. **D.A. Laplagne:** None.

Poster

627. Learning and Memory: Gamma and Theta Activity

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Topic: F.02. Animal Cognition and Behavior

Support: 01DN14018

Title: Respiration-related rhythm and theta oscillations are both present in the olfactory bulb of awake mice

Authors: *V. NGUYEN CHI[1], C. MÜLLER[2], T. WOLFENSTETTER[2], W. ZHONG[2], Y. YANOVSKY[2], A. DRAGUHN[2], A. B. L. TORT[3], J. BRANKACK[2];
[1]Univ. of Heidelberg, Med. Fac., Heidelberg, Germany; [2]Inst. of Physiol. and Pathophysiology, Heidelberg Univ., Heidelberg, Germany; [3]Computat. Neurophysiol., Brain Inst., Natal, Brazil

Abstract: The respiration-related rhythm (RR) in local field potentials (LFP) of the olfactory bulb (OB) has been known for decades. Mice breathe and sniff with frequencies near or within theta range (4-12 Hz). In fact, breathing-related rhythm in the olfactory system has been frequently referred to as theta oscillations. Recently, we demonstrated the existence of an RR in the hippocampus of urethane-anesthetized mice, with frequencies close to theta rhythms (Yanovsky et al., 2014). Respiration-related hippocampal rhythms (HRR) depend on nasal airflow and have a laminar profile and pharmacological properties, clearly distinct from typical theta oscillations. Moreover, RR are most prominent within the dentate gyrus while theta reaches peak power at the hippocampal fissure. Here, we recorded LFP from OB and hippocampus of freely behaving mice. We found two distinct low frequency rhythms (theta and RR) in both structures. Respiration rate, and consequently OB RR and HRR varied from 1.5 Hz during drowsiness to 12 Hz in sniffing mice. Frequently, RR and theta oscillations had overlapping frequencies. However, respiration-induced rhythms could be easily differentiated from theta when respiration rate was below or (in case of sniffing) above the frequency of theta. Furthermore, we observed that gamma oscillations in OB couple exclusively to RR but not to theta. The origin of theta rhythms in the OB is unknown. Our present data show, however, that it is clearly distinct from respiration-related rhythm, which entrain neuronal activity in widespread areas in the rodent brain. References: Yanovsky Y, Ciatipitis M, Draguhn A, Tort ABL, Brankačk J (2014) Slow oscillations in the mouse hippocampus entrained by nasal respiration. J Neurosci 34: 5949-5964.

Disclosures: V. Nguyen Chi: None. **C. Müller:** None. **T. Wolfenstetter:** None. **W. Zhong:** None. **Y. Yanovsky:** None. **A. Draguhn:** None. **A.B.L. Tort:** None. **J. Brankack:** None.

Poster

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Title: Early learning comparison of CA1 and CA3 single-unit response profiles during theta-contingent eyeblink conditioning

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Abstract: Trace eyeblink classical conditioning (tEBC) is known to require the hippocampus for successful acquisition. Our lab has developed a brain-computer interface (BCI) capable of initiating conditioning trials in the presence (T+) or absence (T-) of hippocampal theta, a prominent hippocampal oscillation thought to play a role in coordinating activity across subregions. Utilizing our BCI, previous research has shown theta-contingent changes in CA1 cellular responding during discrete periods of trace tEBC trials, such as the tone and trace intervals, but those studies have not addressed neural activity in hippocampal subregions known to provide essential input to CA1, such as area CA3. In the present study, custom-made drives were used to lower tetrode bundles simultaneously into areas CA1 and CA3 of rabbits (Oryctolagus cuniculus) to analyze response profiles of CA3 pyramidal cells and interneurons relative to CA1 theta-contingent training. When assessing neural spike rate data at different periods of acquisition, we see that both pyramidal cells and interneurons in the T+ condition are more likely to increase their firing than those in T- early in training. Interestingly, we also show that rate increasing CA3 pyramidal cells show a greater magnitude of response in the T+ condition than rate increasing pyramidal cells in the T- condition, a pattern not seen in CA1. These results demonstrate an important difference in cellular activity between areas CA1 and CA3 that could guide future research on how anatomical differences between the two regions contribute to differential roles in associative learning.

Disclosures: **J.J. Cicchese:** None. **S.D. Berry:** None.

Poster

627. Learning and Memory: Gamma and Theta Activity

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CIHR

Title: Local field potential activity in the monkey hippocampus during virtual navigation and contextual learning

Authors: *R. A. GULLI[1,2], G. DOUCET[5,3], B. CORRIGAN[2,5], S. WILLIAMS[4], J. MARTINEZ-TRUJILLO[5,3];
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Abstract: The hippocampus is known to be critical for contextual learning and memory, wherein unrelated aspects of the environment are associated within a singular memory. Several studies in rodents have demonstrated that changes in the firing rate of hippocampal neurons, as well as theta and gamma power are correlated with the formation of these context-dependent associative memories [1,2]. However, activity in the hippocampus of non-human primates may diverge from rodents during contextual learning, since their rate of learning in is much faster than other animal models and they visually explore environments and foveate on objects of interest during comparison and choice processes. Despite this, there have been few examinations of non-human primate hippocampal single-neuron activity and local field potentials (LFPs) recorded during contextual learning. We have created a context-object associative memory task using an open-source video game engine (Unreal Engine 3, Epic Games) remotely controlled via Matlab (Mathworks, Inc.) and recorded hippocampal activity from rhesus monkeys as they freely navigate using a joystick. In this task, monkeys learn a context-dependent object-value hierarchy through trial-and-error while we record hippocampal activity. Similar to previous literature [3,4], we see phase resetting and power peaks in the theta range (4-12 Hz) immediately following saccades as animals navigate the virtual environment. Immediately prior to object presentation in the virtual reality task, hippocampal theta power is elevated, while low gamma (32-64 Hz) is depressed. However, as monkeys saccade between objects in the virtual environment, and navigate towards the ultimately chosen object, this trend is inverted; hippocampal theta power is depressed, with an elevation in low-gamma power. In future analyses, we will explore how these activity patterns evolve over the course of learning, and how they differ between successful and unsuccessful instances of contextual retrieval. These results validate virtual reality environments as learning paradigms for use in non-human primate electrophysiological studies, and provide valuable insight in to the neural dynamics that support context-dependent associative learning in the hippocampus. 1. Komorowski, R. W., Manns, J. R. & Eichenbaum, H. J. Neurosci. (2009). 2.

Tort, A. B. L., Komorowski, R. W., Manns, J. R., Kopell, N. J. & Eichenbaum, H. Proc. Natl. Acad. Sci. (2009). 3. Hoffman, K. L. et al. Front Syst Neurosci (2013). 4. Jutras, M. J., Fries, P. & Buffalo, E. A. Proc. Natl. Acad. Sci. (2013).

Disclosures: R.A. Gulli: None. **G. Doucet:** None. **B. Corrigan:** None. **S. Williams:** None. **J. Martinez-Trujillo:** None.

Poster

627. Learning and Memory: Gamma and Theta Activity

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Title: Reward expectancy modulates CA1 oscillatory dynamics and hippocampal-ventral striatal coupling

Authors: *C. S. LANSINK[1,2], G. T. MEIJER[1], J. V. LANKELMA[1], M. VINCK[1,3], J. C. JACKSON[1], C. M. A. PENNARTZ[1,2];
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Abstract: The formation of place-reward associations depends on the integrity of the hippocampal-ventral striatal system but it is not clear how, at the functional level, the hippocampus connects to this target structure to behaviorally express these associations. When rats navigate through an environment, hippocampal neurons fire in a location-dependent manner, and their activity is temporally organized by a theta rhythm (6-12 Hz) in the local field potential (LFP). Firing patterns of hippocampal CA1 and ventral striatal ensembles during goal-directed navigation were shown to be strongly affected by the presence of reward-predicting cues. We hypothesized that changes in reward expectancy may also impact on rhythmic synchronization in the hippocampus and on the regulation of its long-range neural interactions, such as with the ventral striatum. We explored this hypothesis by analyzing LFPs and single unit activity

simultaneously recorded from the dorsal hippocampal CA1 pyramidal layer, near the hippocampal fissure and the ventral striatum when rats were navigating towards goal-locations. We contrasted goal-site approaches in which reward expectancy was temporarily raised by the illumination of an outcome-predictive cue light, with behaviorally similar approaches that occurred spontaneously; i.e. when cue lights were off. Cued approaches were characterized by a stronger increase in hippocampal oscillatory power in the theta (8-10 Hz) and beta band (16-20 Hz) compared to spontaneous approaches. Remarkably, this increase was not aligned to the onset of the cue but occurred when the rat was on its way towards the goal-site and declined to baseline levels before goal-site arrival. Cued goal-site approaches were furthermore marked by stronger increases in phase-synchrony between hippocampal recording locations and concomitant spike-field phase locking in both frequency bands compared to spontaneous approaches. Reward-expectancy dependent changes in hippocampal rhythmicity were also expressed in the ventral striatum by increased phase modulation of firing rate in both frequency bands in cued compared to spontaneous goal-site approaches. Thus, hippocampal rhythmicity intensifies when reward expectancy is raised by outcome predictive cues and has enhanced impact on ventral striatum, by which the hippocampus- ventral striatal circuitry may claim priority in structures modulating behavioral output to express place-reward associations.

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Poster

627. Learning and Memory: Gamma and Theta Activity

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Compagnia di San Paolo, Progetto d'Ateneo 811M33N

Title: The crosstalk within theta rhythms between secondary auditory cortex and basolateral amygdala is essential during remote fear memory recall

Authors: ***M. CAMBIAGHI**[1], A. GROSSO[1], E. LIKTHTIK[3], R. MAZZIOTTI[4], G. CONCINA[2], A. RENNA[2], T. SACCO[2], J. A. GORDON[3], B. SACCHETTI[2];
[1]Dip. Neuroscienze, [2]Univ. degli Studi di Torino, Torino, Italy; [3]Columbia Univ., New York, NY; [4]CNR - Inst. of Neurosci., Pisa, Italy

Abstract: Negative experiences are quickly learned and long remembered. The secondary auditory cortex (Te2) and the basolateral amygdala (BLA) are both involved in long-term fear memory. Indeed, in auditory fear conditioned rats, secondary auditory cortex is essential for encoding the emotional valence acquired by the auditory stimuli at remote time points. Brain oscillations, particularly the theta rhythm (4-12 Hz), seem to play a crucial role in the memory coding process and connections with amygdala. The present study examined neural activity in Te2 and BLA during the recall of recent and remote fear memories. To this end, we obtained LFP and multi-unit activity (MUA) recordings in Te2 and BLA of rats that underwent recall at 24 hours and 30 days after the association of an acoustic conditioned (CS, tone) and an aversive unconditioned stimulus (US, electric shock). Power spectral analysis of Te2 activity during the recall of aversive memories showed modality-specific significant changes in the theta band, at both 24h and 30 days. In particular, whereas low-theta (3-7 Hz) power increased in both conditions, high-theta (7-12 Hz) power decreased at both recent and remote retrieval. Remote memory recall was also associated with a modality and region specific increase in Te2-BLA low-theta synchrony. Furthermore, MUA recordings confirmed that BLA synchrony with the Te2 correlates with better memory at the remote time-point. Our study demonstrates the functional involvement of Te2 in the expression of auditory fear memory at remote time point.

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Poster

627. Learning and Memory: Gamma and Theta Activity

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Topic: F.02. Animal Cognition and Behavior

Support: FORUM Pharmaceuticals

Title: Effects of α7 nicotinic acetylcholine receptor activation on neurophysiological markers of cognition

Authors: ***M. HAJOS**[1], C. KELLEY[1], D. NAGY[1], L. LEVENTHAL[2], M. STOILJKOVIC[1]; [1]Comparative Med., Yale Univ. Sch. of Med., New Haven, CT; [2]FORUM Pharmaceuticals, Watertown, MA

Abstract: Experimental and clinical findings demonstrate that pharmacological activation of α7 nicotinic acetylcholine receptors (α7 nAChRs) improves cognitive function. In the present study effects of the novel α7 nAChRs agonist, FRM-17874 ((R)-7-fluoro-N-quinuclidin-3-yl)benzo [b]thiophene-2-carboxamide), an analogue of encenicline, was evaluated on neurophysiological markers related to cognition. One of the particular aims was determining the effective dose-range of the compound, supporting its pharmacokinetic-pharmacodynamic analysis. Since it has been shown that α7 nAChR agonists modulate neuronal network oscillation, efficacy of FRM-17874 was determined on elicited hippocampal theta oscillation in C57BL/6 mice and Wistar rats under urethane anesthesia. Using this assay, previous studies showed that drugs disrupting cognitive function eliminate or decrease the power of elicited theta oscillation, whereas drugs used to treat Alzheimer's disease, including acetylcholinesterase inhibitors and memantine, augment the power of theta activity. FRM-17874, administered subcutaneously at 0.1, 0.3, 1, 3 and 10 mg/kg showed a dose-dependent facilitation of the power of stimulation-induced hippocampal theta oscillation both in mice ($F(5,26) = 10.64$, $p < 0.0001$) and rats ($F(4,29) = 6.297$, $p < 0.001$) compared to the saline control groups. FRM-17874 significantly enhanced theta power at 1 and 3 mg/kg doses in mice, and at 0.3 and 1 mg/kg doses in rats, resulting an approximately 30 - 40% increase in absolute theta power both in rats and mice. Although there was a slight difference in the effective doses between mice and rats, their drug exposure levels in the brain were fully overlapping, indicating a species difference in pharmacokinetics. In a subsequent study, efficacy of FRM-17874 was determined on synaptic plasticity within the subiculum-medial prefrontal cortex pathway. Long-term potentiation (LTP) was generated by tetanic stimulation of subiculum in urethane anesthetized male rats. Compared to saline controls, FRM-17874 significantly increased LTP ($F(3,16) = 10.388$, $p < 0.0005$) at 0.3 and 1 mg/kg, s.c. but not at 3 mg/kg. Considering the physiological role of hippocampal theta oscillation in mnemonic functions and memory formation, and the role of the hippocampal - prefrontal cortex pathway in working memory, the described neurophysiological effects could be contributing mechanisms underlying the cognitive effects of α7 nAChR activation. However, the relatively narrow effective dose-range in these assays further underscores the critical importance of pharmacokinetics and dose-selection for clinical treatment.

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Poster

627. Learning and Memory: Gamma and Theta Activity

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Support: Academy of Finland Grant 275954

Title: Hippocampal theta phase -contingent memory retrieval across trace eyeblink conditioning in rabbits

Authors: *T. WASELIUS, M. PENTTONEN, J. WIKGREN, M. S. NOKIA;
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Abstract: The hippocampal theta oscillations (3-12 Hz) play a prominent role in learning in mammalian brain. According to the theory of Hasselmo, Bodelón and Wyble (Neural Computation, 14(4):193-817, 2002) the phase of the theta cycle determines the optimal time windows for encoding and retrieval of memories: Encoding is favored at fissure theta trough and retrieval at fissure theta peak. In line with this notion, in our recent study on trace eyeblink conditioning in rabbits we found that the timing of the conditioned stimulus (CS) based on the theta phase affects hippocampal responses and learning. Namely hippocampal responses to CS were most synchronized when presented on fissure theta trough. Learning was retarded when the CS was presented at theta peak. However in contradiction to the theory our results suggested that in well-learned subjects the memory retrieval and performance of the conditioned eyeblink is not dependent on the theta phase regardless of a clear effect on neural responses. Here, we tested the effects of hippocampal theta phase-contingent stimulus presentation on memory retrieval across the whole conditioning process. We trained adult female New Zealand white rabbits in trace eyeblink conditioning using a tone CS and a 100-ms air puff unconditioned stimulus. The trace period was 500 ms. Preliminary results indicate that the phase of theta at CS onset has no effect on the performance of the behavioral learned response in any stage of trace eyeblink conditioning, when a 200-ms tone is used as a CS. This result is consistent with our earlier finding and suggests that retrieval of recently acquired memories and consequently performing a learned response is moderated by neural mechanisms other than hippocampal theta. However, using a CS longer than the duration of a single theta cycle might not be optimal for the effects studied. The data presented will indicate whether the effects of theta phase on memory retrieval during trace eyeblink conditioning are dependent on the timing and/or duration of the CS.

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Poster

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ANR-10-IAIHU-06

Title: Functional ultrasound imaging of a spatial navigation task in mobile rat

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Abstract: Hippocampal theta rhythm is the electrophysiological signature of active locomotion during spatial navigation. It is critically involved in spatial memory, both during a task and subsequent sleep, and also plays a role in hippocampal-cortical interactions. Using functional ultrasound imaging (fUS) we sought to reveal the metabolic events associated with locomotion theta in mobile rats. We recorded from rats walking along a linear maze, to address how brain-wide networks activate during periods of hippocampal theta rhythm. Healthy Sprague Dawley rats ran on a 2.25m long, 0.2m wide linear track for water reward. A single imaging plane included dorsal hippocampus, cortex with somatosensory areas, and thalamus. In order to temporally resolve hemodynamics as the animal crossed the maze fUS compound frames were acquired at 500Hz for 12s. Acquisition was triggered when the animal turned around, and was followed by a 40s lapse to collect the data. As expected, hippocampal theta was consistently associated with locomotion. Distance travelled over time was slower (56-64%) than in control, surgery-free, rats ($p<10^{-6}$). Yet, maximum speed was only slightly slower for the initial 15min, with the difference reducing to non-significant 1% thereafter. In order to analyze series of track crossing trials, we aligned them by setting each trial reference time when the rat crossed the middle of the maze. Hemodynamic changes ranged from -10 to +20%. As expected, theta band intra-hippocampal EEG power peaked at top animal speed, which was coincident with crossing the midline, with a mid-height theta peak width of 3.2+/-0.3s (n=8). In order to quantify functional activation during the task, we computed the maps of Pearson's correlation coefficient between power in the theta band and pixel intensity, for varying time lags. Averaging pixels across anatomical areas revealed hyper-perfusion in the somatosensory cortex, dorsal thalamus

and hippocampus, and hypo-perfusion in the ventral thalamus. These correlations were consistent with fUS signal time course. Hyperemia peaked at 0.7-1.5s following the peak of hippocampal theta, which is compatible with signaling cascades that adapt blood flow to processing activation. Our data reveal a pattern of combined hippocampal and widespread cortical activation in a short time window around the navigation task, with coordinated dorsal thalamic activation and ventral thalamus suppression.

Disclosures: A. Bergel: None. **L. Sieu:** None. **E. Tiran:** None. **T. Deffieux:** None. **M. Pernot:** None. **J. Gennisson:** None. **A.C. Bonnot:** None. **M. Tanter:** None. **I. Cohen:** None.

Poster

627. Learning and Memory: Gamma and Theta Activity

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 627.12/AA32

Topic: F.02. Animal Cognition and Behavior

Support: NSF 0090451

Title: Laminar, sub-regional, areal and behavioral contributions to variability in the hippocampal speed-theta relationship

Authors: *L. L. LONG, J. J. CHROBAK;
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Abstract: Theta (6-12 Hz) rhythmicity in the local field potential (LFP) reflects a clocking mechanism that brings physically isolated neurons together in time, allowing for the integration and segregation of distributed cell assemblies. Variation in the theta signal has been linked to locomotor speed, sensorimotor integration as well as cognitive processing. Previous research has characterized the decrease in the speed-theta power relationship across the septotemporal axis of the hippocampus. Here, we take previous studies a step further and investigate other sources of variability in the speed-theta relationship including laminar, sub-regional (e.g., DG vs. CA1), as well as behavioral differences observed across experiments (e.g., linear track vs. open field running). Rats were simultaneously outfitted with septotemporal and entorhinal cortical placements and recordings were obtained over a wide variety of experimental settings. Previously published data as well as current findings indicate robust variability in the speed-theta relationship as a function of laminar, sub-regional, areal and behavioral output of the animal. While preliminary, the current findings suggest that the hippocampal theta signal is not a limited information source and exhibits significant variation as a function of the aforementioned. Here,

we speculate that the speed-theta relationship represents the flow of sensory input across hippocampal circuitry and it appears that speed "synchronizes" hippocampus circuits. Alterations in the strength and "scaling" of the speed-theta relationship across the septotemporal axis of the hippocampus could be reflective of hippocampus processing with high speed-theta relationships indicating efficient processing on shorter time-scales (e.g., septal hippocampus), whereas low speed-theta relationships indicating processing on longer time-scales (e.g., temporal hippocampus). These ideas are consistent with increases in place field size across the septotemporal axis of hippocampus along with the possibility that septal hippocampus processes details of the proximal spatiotemporal environment, while more temporal aspects process larger spaces and wider time-scales. Thus, emergent function across the three-dimensional expanse of the hippocampus varies with respect to spatiotemporal scale. Overall, a better understanding of the relative contribution of these quantifiable variables and their variation as a function of environmental conditions and electrode location should facilitate our understanding of the relationship between theta and sensorimotor/cognitive functions.

Disclosures: L.L. Long: None. **J.J. Chrobak:** None.

Poster

627. Learning and Memory: Gamma and Theta Activity

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Topic: F.02. Animal Cognition and Behavior

Support: Research Grants Council of Hong Kong (CUHK479213)

Title: Effects of adenosine A2A receptor activation on chronic intermittent hypoxia-induced changes in sleep architecture and synaptic plasticity in rat

Authors: *L. DU, L. XU, Y. KE, W.-H. YUNG;
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Abstract: Intermittent hypoxia and sleep disturbance associated with obstructive sleep apnea (OSA) are known to contribute to central nervous system dysfunction, including learning and memory impairment. Based on an OSA model in which rats were subject to daily 8-hr cycles of oxygen between 18% and 8% every 90s, we investigated the impact of OSA-associated intermittent hypoxia (IH) per se on sleep architecture. We also studied the effects of activation of adenosine A2A receptor, which is known to be involved in sleep control as well as hippocampal synaptic plasticity, on our model. We found a decrease in total sleep time and increased sleep

fragmentation induced by chronic IH. Administration of the A2A receptor agonist CGS21680 tended to reduce sleep fragmentation index and increased power of theta rhythm during non-REM sleep. At the same time, CGS21680 could also rescue IH-induced impairment in hippocampal long-term synaptic plasticity. Together, these results suggest that severe IH could affect sleep architecture and activation of adenosine A2A receptor is beneficial in ameliorating OSA-associated neurocognitive deficits.

Disclosures: **L. Du:** None. **L. Xu:** None. **Y. Ke:** None. **W. Yung:** None.

Poster

627. Learning and Memory: Gamma and Theta Activity

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Program#/Poster#: 627.14/AA34

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant MH100820

Title: Theta-rhythmic drive between medial septum and hippocampus during theta and non-theta states: A Granger causality analysis

Authors: *D. KANG[1], M. DING[1], I. TOPCHIY[2], L. SHIFFLETT[2], B. KOCSIS[2];
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Abstract: Medial septum (MS) plays a critical role in controlling the electrical activity of the hippocampus (HIPP). In particular, theta rhythmic burst firing of MS neurons is thought to drive lasting HIPP theta oscillations in rats during waking motor activity, and REM sleep. Less is known about MS-HIPP interactions in non-theta states such as slow wave sleep (SWS) and quiet waking, although it was noted in early reports that MS burst activity may remain unchanged during non-theta states when HIPP theta rhythm is temporally replaced by other type of activity. The present study used Granger causality (GC) to identify the direction of rhythmic influence between MS and HIPP within the theta frequency band during theta and non-theta states. We categorize REM sleep and exploration as theta states while SWS and quiet waking (QW) are categorized as non-theta states. MS neuron firing was recorded using three tetrodes connected to separate microdrives in freely moving rats, along with HIPP field potentials and neck muscle EMG. MS neurons (>50) were identified in 4 rats using principal component and K-means clustering algorithms. Spectral analysis included autospectra of HIPP field potentials, and MS neuron firing, as well as MS-HIPP coherence and GC in both MS->HIPP and HIPP->MS

directions using a non-parametric algorithm specifically developed for handling point processes (spike trains). We found that during non-theta states, while GC revealed a unidirectional MS->HIPP influence over a wide frequency band (2-10 Hz, maximum: ~8Hz), there was no theta peak in the hippocampal power spectra, indicating a lack of theta activity in HIPP. In contrast, during theta states, theta peaks were seen in both MS and HIPP power spectra, and were accompanied by bidirectional GC with MS->HIPP and HIPP->MS theta drives being of equal magnitude. Thus, GC in non-theta states vs. theta states primarily differed in the level of HIPP->MS. The present findings suggest a modification of our understanding of the role of MS as the ultimate theta generator in two regards. First, a MS->HIPP theta drive does not necessarily induce theta oscillations in the hippocampus, as found in non-theta states. Second, HIPP theta oscillations involve bidirectional rhythmic interactions between MS and HIPP during theta states.

Disclosures: **D. Kang:** None. **M. Ding:** None. **I. Topchiy:** None. **L. Shifflett:** None. **B. Kocsis:** None.

Poster

627. Learning and Memory: Gamma and Theta Activity

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Program#/Poster#: 627.15/AA35

Topic: F.02. Animal Cognition and Behavior

Support: ANR-13-NEUC-0005-01

Title: Activity of supramammillary nucleus neurons during theta and slow oscillations in anaesthetized rats

Authors: *A. SLEZIA[1,2], A. F. VICENTE[1,2], A. KASZAS[1,2], A. GHESTEM[1,2], P. P. QUILICHINI[1,2], C. BERNARD[1,2];
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Abstract: Theta oscillations in the hippocampus, entorhinal and subicular cortices are critical in a variety of mnemonic processes. Theta oscillations are strongly modulated by the medial septum, and the supramammillary nucleus of hypothalamus. Theta oscillations are an emergent property of cortical and subcortical structures, and the exact role of the supramammillary nucleus of hypothalamus in theta genesis and modulation is not fully understood. In our study, we combined local field recordings and single cell recordings with silicon probes and juxtacellular

electrodes to assess the behavior of neurons from the supramammillary nucleus, together with silicon probe recordings in the hippocampus during theta oscillations, as well as during slow oscillations for comparison in anaesthetized rats. We characterized supramammillary nucleus neurons on the basis on their firing properties and on the basis on their phase correlation with respect to theta and slow oscillations. Our preliminary result shows that supramammillary nucleus contains cells with different firing properties and also different phase relationship to theta and slow oscillations. We suggest that such a heterogeneous collection of neuronal firings may be instrumental in the pacing of oscillatory activities.

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Poster

628. Learning and Memory: Aging III

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 628.01/AA36

Topic: F.02. Animal Cognition and Behavior

Support: BBSRC PNNDAGA

Title: Altered synaptic and molecular mechanisms of memory formation in ageing

Authors: ***W. AZIZ**[1], I. KRAEV[2], K. MIZUNO[1], F. A. VIGIL[1], K. KASBI[1], S. ROTHE[1], A. AHMAD[1], M. STEWART[2], K. P. GIESE[1];
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Abstract: Normal ageing is associated with deficits in learning and memory, which depends on the hippocampus. Impairments in induction and maintenance of long-term potentiation (LTP) in hippocampal area CA1 are thought to contribute to age-associated learning and memory impairments. However, despite these age-related LTP impairments memories can be formed with repeated training trials. Little is known about alternate synaptic mechanisms underlying this memory formation in ageing when LTP is impaired. Here, we used a hippocampus-dependent task called contextual fear conditioning (CFC) and used aged (18 months) and young mice (3 months). We showed that by increasing the stimulus intensity (5 shocks) the aged mice can make a memory distinct from that when presented with 1 or 2 shocks. Despite their ability for memory formation, aged mice had impaired autophosphorylation of alphaCaMKII at site T286 (pT286 αCamKII), a molecular signature of LTP. Young mice showed normal up-regulation of pT286

αCaMKII after CFC training. Using electron microscopy we found that young animals show an increase in mushroom spines after training. These are considered to be mature spines recruited for stabilizing a LTP dependent memory. In contrast to young mice, we did not observe an increase in mushroom spines in aged mice after 5 training trials. Next, we investigated the role of postsynaptic density protein-95 (PSD-95), a critical protein for activity-dependent synaptic remodeling associated with synaptic plasticity, and its correlation with structural alterations in ageing synapse. We found a specific up regulation of PSD-95 in aged mice after 5 training trials. Moreover, electron microscopy revealed generation of special type of spines called multi-innervated spine (MIS) specifically in aged mice after training. MIS are formed by contact of one spine with typically two excitatory presynaptic partners. Our results showed in detail that LTP dependent memory mechanisms are indeed lacking at molecular and synaptic level in aged mice. We propose that PSD-95 dependent up-regulation of MIS provides an alternative mechanism to make memories during ageing.

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Poster

628. Learning and Memory: Aging III

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Topic: F.02. Animal Cognition and Behavior

Support: NIA R37AG036800

Evelyn F. McKnight Brain Research Foundation

Title: Region specific expression of aging and cognitive genes

Authors: ***L. IANOV**, A. RANI, A. KUMAR, B. S. BEAS, J. L. BIZON, T. C. FOSTER; Neurosci., McKnight Brain Institute, Univ. of Florida, Gainesville, FL

Abstract: Cognitive decline during aging and neurodegenerative disease are associated with senescence of specific brain regions including the hippocampus and the medial prefrontal cortex (mPFC). However, there is enormous variability in cognitive decline, suggesting differential aging of processes critical to memory. Similar to aging humans, aged rodents exhibit variability in behavioral performance on a number of tasks that depend on the hippocampus or mPFC. While it is understood that gene expression profiles differ with age, studies are needed to

determine if specific transcriptional profiles in these brain regions relate to cognitive function during aging. To address this question, the current study utilized a powerful combination of a battery of behavioral tasks that are sensitive to different cognitive processes that decline with age and next-generation sequencing of the transcriptome (RNA-seq) in young (5-7 months) and aged (23-25 months) male Fischer 344 rats. Age effects: The results indicate that aging in the mPFC was associated with a decrease in expression of genes for gene ontology clusters linked to synaptic markers and chromatin assembly and disassembly genes ($p<0.05$). For hippocampal genes, aging was related with an increase in immune response genes and a decrease in genes linked to synaptic transmission and neural activity. Cognition-related genes: Re-exposure to the light chamber, 24 hours after inhibitory avoidance acquisition, increased expression of stress response and immediate early genes in the mPFC and hippocampal CA1 region indicating that both regions are responsive to experience. Impairment in a mPFC-dependent task, set-shifting, was correlated with decreased expression of mitochondrial function genes in the mPFC of aged rats ($p<0.05$). Impaired spatial episodic memory (water maze) in aged rats was correlated with decreased expression of synaptic and neural activity genes (e.g. Grin2b, Lin7a, Gria1, Egr1-3). Overall, relatively, few genes in the hippocampus and mPFC correlated with set-shifting and water maze performance, respectively, indicating that differential expression correlated with behavior was specific for brain regions that mediate the behaviors examined. Together, these results show that the identified clusters of genes within specific brain regions may explain the variability present in cognitive decline during aging.

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Poster

628. Learning and Memory: Aging III

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Support: NIH/NIMH R01MH096816

NIH/NINDS R01NS076708

DOD AR120254

Title: The role of mTORC2 in age-associated memory loss

Authors: *J. L. JOHNSON[1,2], W. HUANG[2], G. ROMAN[3], M. COSTA-MATTIOLI[2]; [2]Memory and Brain Res. Ctr., [1]Baylor Col. of Med., Houston, TX; [3]Biol. and Biochem., Univ. of Houston, Houston, TX

Abstract: As our population ages, cognitive decline and dementia are becoming more prevalent. The fact that memory declines as a function of age indicates that there must be crosstalk between components of these two processes. Yet, the molecular mechanisms underlying these inevitable processes are not fully understood. Although the serine/threonine kinase mechanistic target of rapamycin (mTOR) has long been implicated in aging, its role in brain aging remains unclear. Given the evolutionary conservation of mTOR between fruit flies and humans, we investigated the specific role of the new mTOR complex 2 (mTORC2) in age-related memory impairment in both the fly and rodent. We show that the activity of mTOR complex 2 (mTORC2) declines with age in the brain of both fruit flies and mice Interestingly, treatment with a small molecule that activates mTORC2 restores mTORC2 activity and rescues long-term memory (LTM) deficits in both aged mice and flies. In addition, we found that pharmacologically activating mTORC2 or promoting actin polymerization enhances long-term memory. In contrast to the current approaches to reverse memory loss that have primarily focused on changes in gene expression at the epigenetic and transcriptional level, our data suggests a novel, evolutionarily conserved mechanism for restoring memory that is dependent on structural plasticity. Although we are only beginning to understand the unique functions of mTORC2 in the brain, therapeutic approaches targeting the mTORC2 signaling pathway may have a profound impact in the prevention and treatment of age-related neurological diseases.

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Poster

628. Learning and Memory: Aging III

Location: Hall A

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Program#/Poster#: 628.04/AA39

Topic: F.02. Animal Cognition and Behavior

Title: Dorsal but not ventral hippocampal volume predicts cognitive performance in age

Authors: *J. M. REICHEL[1], B. T. BEDENK[2], M. CZISCH[2], C. T. WOTJAK[2]; [1]Albert Einstein Col. of Med., Bronx, NY; [2]Stress Neurobio. and Neurogenetics, Max Planck Inst. of Psychiatry, Munich, Germany

Abstract: Cognitive decline with progressed age is a common phenomenon as well as morphological changes in the CNS occurring over the life span. However, not all aged individuals or rodents develop cognitive decline regardless of morphological changes. Here, we performed repeated within-subject testing of male mice in spatial learning tasks and subsequent manganese-enhanced MRI analyses at the ages of 8, 16 and 24 months in order to establish a timeline and correlation between morphological changes in ageing CNS and cognitive performance. Based on their spatial learning abilities at the age of 24 months we separated the mice in good and bad performers. For both groups we observed an increase in absolute whole brain volume over time accompanied by a decrease in total hippocampal volume. However, when normalized to the whole brain volume, the relative hippocampal volume, in particular the relative dorsal hippocampal volume, decreased significantly more for mice with poor spatial learning abilities is age. Moreover, we found that good- and bad performer had an a priori difference in their relative dorsal hippocampal volume at 8 months. Interestingly, we observed no behavioral differences between the groups until the age of 16 months, indicating a possible threshold connecting dorsal hippocampal volume and spatial learning performance.

Disclosures: **J.M. Reichel:** None. **B.T. Bedenk:** None. **M. Czisch:** None. **C.T. Wotjak:** None.

Poster

628. Learning and Memory: Aging III

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Topic: F.02. Animal Cognition and Behavior

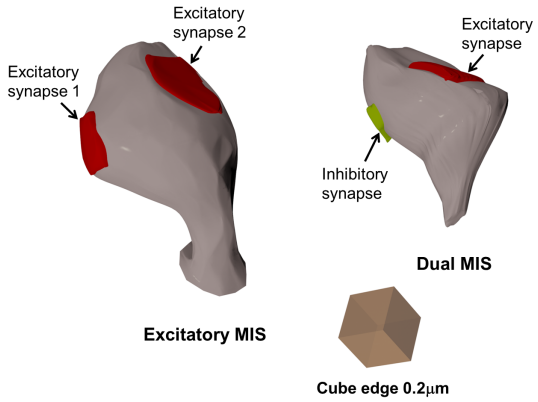
Support: BBSRC Grant

Title: Morphological changes in synapses during memory formation in ageing

Authors: *I. V. KRAEV[1], A. KIRBY[1], W. AZIZ[2], K. MIZUNO[2], H. A. DAVIES[1], P. GIESE[2], M. G. STEWART[1];
[1]The Open Univ., Milton Keynes, United Kingdom; [2]King's Col. London, London, United Kingdom

Abstract: Long-term memory formation is related to functional strengthening of synapses. If the functional strengthening is impaired, hippocampus-dependent memory formation depends on modification of neural circuits and in particular the generation of multi-innervated dendritic spines (MIS) (Radwanska et al., 2011). Aged-related memory decline is associated with synaptic strengthening impairment. Memory formation in older animals is slower and less flexible in

comparison to younger animals. We have analysed MIS generation in the hippocampus before and after contextual fear conditioning (CFC) in the following wild-type groups of C57BL6N female mice: •young adult (n=6, 3 months): (i) naïve and (ii) 24 hours after CFC; •aged mice (n=4, 18 months): (i) naïve,(ii) 2 hours and (iii) 24 hours after CFC. Mice were perfused intracardially and brain slices taken for electron microscopy, 3D reconstructions from serial ultrathin sections were performed to allow quantitative analyses of structural changes in dendritic spines and post-synaptic densities in hippocampal CA1 stratum radiatum. Two MIS types were analysed: excitatory, which has more than one excitatory input from different axons; and dual, has one excitatory and one inhibitory contact (see Fig.1). We showed that number of mushroom spines increased after training in young but not aged mice. Furthermore there was a greater overlap between classes of thin and mushroom spines in young mice after training indicating that maturation process has occurred. On the other hand, aged mice showed a separation between thin and mushroom spines and an increase in the number of large thin spines not yet transformed into mushroom spines. Excitatory MIS analysis showed that the number of MIS was significantly higher in aged naïve mice compared to young naïve mice. Moreover, training induced a significant increase in MIS number in aged but not young mice. Inhibitory synapse analyses showed that both aged and young mice had an increased percentage of inhibitory synapses after training, due to an increase in number of dual MIS, but not shaft inhibitory synapses.



Disclosures: **I.V. Kraev:** None. **A. Kirby:** None. **W. Aziz:** None. **K. Mizuno:** None. **H.A. Davies:** None. **P. Giese:** None. **M.G. Stewart:** None.

Poster

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Title: Epigenetic modification of PKMζ rescues aging-related cognitive impairment

Authors: C. CHEN[1,2], S.-Q. MENG[1,2], Y.-X. XUE[2], C.-Y. SUN[1,2], J.-H. DENG[1,2], N. CHEN[2], Y.-P. BAO[2], L.-L. CAO[3], W.-G. ZHU[3], *Y. LUO[4], J. SHI[2], W.-H. SONG[5], L. LU[1,2,6];
[1]Inst. of Mental Health, Peking Univ. Sixth Hospital, and Key Lab. of Mental Hlth., Beijing, China; [2]Natl. Inst. on Drug Dependence and Beijing Key laboratory of Drug dependence Research, Peking Univ., Beijing, China; [3]Dept. of Biochem. and Mol. Biology, Peking Univ. Hlth. Sci. Ctr., Beijing, China; [4]Dept. of pharmacy, Med. Sch. of Hunan Normal Univ., Changsha, China; [5]Brain Res. Centre, Departments of Med. and Psychiatry, Univ. of British Columbia, Vancouver, BC, Canada; [6]Peking-Tsinghua Ctr. for Life Sci. and PKU-IDG/McGovern Inst. for Brain Research, Peking Univ., Beijing, China

Abstract: Background: Cognition is impacted by aging. However, the mechanisms that underlie aging-associated memory impairment are unclear. PKMζ is a crucial molecule involved in the maintenance of long-term memory. Experiential learning and environmental stimulation have powerful influence on individual learning ability by mediating epigenetic modification of genes and further transcription and translation. Nevertheless, the transcription regulating mechanisms of PKMζ in memory retention are unclear. Here we explored whether the aberrant methylation of PKMζ DNA in the prelimbic cortex (PrL) is involved in aging-related memory decline. Methods: Rats were divided into three groups: young rats, adult rats and aged rats. We confirmed aging-related cognitive impairment by three types of behavior models which include contextual fear memory, Morris water maze and novel object recognition. We detected the expression of relative proteins in PKMζ-GluR2 signaling pathway in mPFC when LTM retention was impaired in aged rats. Then, we detected mRNA and DNA methylation levels of pkmζ respectively, in mPFC during the time that LTM impairment in aged rats. Next, we explored the reversing effect of EE on aging-related cognitive impairment and detected relative proteins expression in PKMζ-GluR2 signaling pathway, pkmζ mRNA and pkmζ methylation levels. Results: We confirmed that aged rats exhibited cognitive impairment in memory retention test 24 h after training compared with adult and young rats and genetic overexpression of PKMζ in the PrL rescued cognitive impairment in aged rats. After fear conditioning, the protein levels of PKMζ and the membrane

expression of GluR2 increased in the PrL in young and adult rats but not in aging rats, and the levels of methylated pkmζ DNA in the PrL decreased in all age groups, whereas the levels of unmethylated pkmζ DNA increased only in young and adult rats. Next, we found that 16 weeks environmentally enriched housing restored cognitive performance in aged rats in the three different behavior models. Environmentally enriched housing augmented PKMζ and GluR2 protein levels and PKMζ mRNA levels in PrL area of aged rats. The methylated DNA levels of pkmζ were decreased and unmethylated levels of pkmζ were increased in PrL area of aged EE rats. These rescuing effect of environmentally enriched housing can be reversed by microinjecting DN-PKMζ or antisense oligodeoxynucleotide of PKMζ in PrL area in aged rats. Conclusion: These results indicated that PKMζ may be a potential target for the treatment of aging-related cognitive impairment.

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Poster

628. Learning and Memory: Aging III

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 628.07/AA42

Topic: F.02. Animal Cognition and Behavior

Title: Gross anatomical correlates of age-related spatial-cognitive decline in homing pigeons (Columba livia)

Authors: *V. J. COPPOLA, A. J. SCHREIBER, N. KANYOK, V. P. BINGMAN; Psychology, Bowling Green State Univ., Bowling Green, OH

Abstract: There is a growing interest in age-related cognitive decline in birds. For example, we recently investigated spatial-feature reference memory ability in older pigeons (11-14 years) and younger pigeons (2-3 years). In this task, pigeons were to learn which feeder, in an array of eight feeders, contained a food reward. Feeders could be distinguished from one another by their unique feature cues *and* spatial location, both of which remained stable across all training trials. It was found that older pigeons required a greater number of choices and sessions to reach the training criterion, and were less accurate with their first choice on each trial. It was concluded that older pigeons are impaired in the acquisition of reference memory, even when afforded two reliable cues (one spatial; one visual) for encoding. In the current study we began the search for neural correlates of cognitive decline in ten homing pigeons (5 young; 5 old) that previously

served as subjects on the spatial-feature reference memory task. Three linear, orthogonal measurements (i.e., anterior-posterior, dorsal-ventral, and medial-lateral) were taken of the forebrain and cerebellum, and the smallest possible cubic volume that could contain each structure was calculated. Additionally, two orthogonal measurements (anterior-posterior and dorsal-ventral) were taken of both the left and right tectum to obtain the smallest possible squared area that could be formed around each structure. It was found that only the forebrain was significantly smaller in older pigeons; the average cubic volume of the older pigeons' forebrain was 5.6% smaller than that of the younger pigeons. Furthermore, when assessed independent of age, cubic volume of the forebrain significantly correlated with measures of spatial-feature reference memory acquisition. Taken together, these results suggest that a reduction in forebrain volume may in part explain observed age-related cognitive deficits in homing pigeons.

Disclosures: V.J. Coppola: None. **A.J. Schreiber:** None. **N. Kanyok:** None. **V.P. Bingman:** None.

Poster

628. Learning and Memory: Aging III

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 628.08/AA43

Topic: F.02. Animal Cognition and Behavior

Support: NIH DP5 OD017908

NIH T32 MH015174

Title: Behavioral deficits in a mouse model of Alzheimer's disease are mediated by alterations in immediate early gene expression

Authors: *J. PERUSINI, S. CAJIGAS, S. C. LIM, C. A. DENNY;
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Abstract: Alzheimer's disease (AD) is a highly prevalent neurodegenerative disorder characterized by amyloid-beta (Aβ) peptides (plaques) and tau (neurofibrillary tangles). Mice with both the APPswe and PS1dE9 mutant transgenes have been previously developed and are characterized by early plaque development, around 4-6 months of age. While this line has been commercially available for some time, little is known behaviorally about these mice. We have performed a battery of behavioral assessment tests in order to better understand these mice for use in Alzheimer's disease models at four different time points both pre- and post-plaque

development. We tested anxiety-like, depressive-like, social, spatial, and cognitive behaviors. While AD mice showed no anxiety or depressive-like phenotypes, social and cognitive deficits emerged around 6 months, as tested by social recognition (SR), novel object recognition (NOR), Y-maze, and contextual fear conditioning (CFC) paradigms. By 8 months of age, however, wild-type mice also showed deficits in these cognitive tasks. These studies show that with increasing plaque load in the hippocampus, cognitive impairments emerge earlier than do age-related impairments.

Disclosures: **J. Perusini:** None. **S. Cajigas:** None. **S.C. Lim:** None. **C.A. Denny:** None.

Poster

628. Learning and Memory: Aging III

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 628.09/AA44

Topic: F.02. Animal Cognition and Behavior

Support: CONACYT 155242

PAPIIT IN209413/24

PAPIIT IN212013

Title: Aged-dependent effect of histone deacetylase inhibition on synaptic plasticity and memory

Authors: ***G. RAMIREZ MEJIA**[1], P. MORENO-CASTILLA[1], L. RODRIGUEZ-DURAN[2], M. ESCOBAR[3], F. BERMUDEZ RATTONI[1];
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Abstract: Epigenetic regulation, including histone acetylation plays an important role for long-term memory formation. The increase of histone acetylation using unspecific histone deacetylases inhibitors (HDACi) enhances memory consolidation for hippocampus-dependent tasks and rescues age-related memory impairments. However the effect of HDACi in non-hippocampal memory in age-related memory impairments remain unexplored. The aim of this work was to study the effect of HDACi MS-275 on neocortical synaptic plasticity and memory in young and aged mice. We used young- and aged- B6129SF2/J mice and we performed *in vivo* electrophysiological recordings in anesthetized animals receiving intracerebral injections of MS-275 at insular cortex (IC) prior induction of long-term potentiation (LTP) in the basolateral amygdala-insular cortex (BLA-IC) projection. High frequency stimulation was applied into the

BLA, responses were measured at IC. The effect of the HDAC inhibitor in memory performance was evaluated in animals administered with MS-275 or vehicle, bilaterally in the IC prior to acquisition of conditioned taste aversion (CTA) or prior to object recognition memory (ORM). We found that HDACi showed increase induction of LTP, this change was more pronounced in aged than young mice. Also the MS-275 showed age-dependent effect of HDAC inhibition over memory process. In young animals there were no changes in extinction of CTA while in aged animals the HDACi produced a delay in extinction process. In the case of ORM the HDACi impairs recognition memory in young animals while in aged animals reestablish this memory. Our findings suggest that there is age-dependent regulation about histone acetylation induced by specific HDAC inhibitor and study of this process could help to understand memory alterations in aging.

Disclosures: G. Ramirez Mejia: None. **P. Moreno-Castilla:** None. **L. Rodriguez-Duran:** None. **M. Escobar:** None. **F. Bermudez Rattoni:** None.

Poster

628. Learning and Memory: Aging III

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 628.10/AA45

Topic: F.02. Animal Cognition and Behavior

Title: A biophysical, minimal model to explore age-related changes in ion channel gene expression and excitability in CA1 pyramidal cells

Authors: *E. MCKIERNAN[1], M. A. HERRERA-VALDEZ[2], D. F. MARRONE[1];
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Abstract: As we age, our brains undergo a variety of changes, and yet we understand relatively little about these processes. What does normal neurophysiological aging look like and what are the various stages? How does the electrical activity of neurons change? How do aging neurons respond to input from other cells? Answering these questions is not just fundamental to understanding aging as a neurophysiological process, but also to understanding how this process goes awry in age-related disorders of clinical importance such as Alzheimer's disease. Many studies of aging have focused on the hippocampus, an area of the brain involved in learning and memory formation. Studies indicate that behavioral impairments and plasticity changes result in part from altered excitability in aged pyramidal cells. Pyramidal cells from aged animals show decreased excitability, increased spike frequency adaptation, and larger afterhyperpolarization

currents compared to neurons from young animals. Despite extensive study, however, it is still not well understood how changes in hippocampal pyramidal cell excitability and ion channel gene expression may affect neuron responsiveness to inputs and microcircuit output. We present a biophysical, minimal mathematical modeling approach to understand more about the effects of aging on hippocampal cellular responses. We show how small changes in gene expression in model CA1 pyramidal cells can reproduce the electrophysiological markers of aging, and link these changes to a geometrical analysis of the bifurcation structure of these neurons. This bifurcation analysis allows us to demonstrate how shifting the balance of ion currents can lead to functionally equivalent and non-equivalent cells.

Disclosures: **E. McKiernan:** None. **M.A. Herrera-Valdez:** None. **D.F. Marrone:** None.

Poster

628. Learning and Memory: Aging III

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 628.11/AA46

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant K99 AG044469

grant from the BrightFocus Foundation

Title: Dissociation of memory and long-term potentiation performance in aged mice

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Abstract: Long-term potentiation (LTP) is widely considered as a synaptic model for memory. In general, LTP can be divided into two distinct forms: early LTP (E-LTP), which is transient and requires posttranslational mechanisms; late LTP (L-LTP), which is dependent on new protein synthesis. To our knowledge, the relationships between different forms of LTP and memory performance during aging process have not been elucidated. In the current study, by taking approaches of electrophysiology and behavioral tests, we compared LTP and memory performance in young (5 - 6 months of age) and old (18 - 20 months of age) mice. Compared to young mice, the old mice exhibited impaired memory as assessed by hidden platform Morris Water maze, Y water maze, and novel object recognition tests. In contrast, hippocampal L-LTP

(induced by two-train high frequency stimulation, HFS) in old and young mice was not distinguishable. However, E-LTP (evoked by one-train HFS) was significantly reduced in old mice, compared to those in young ones. Our results suggest that dissociation of memory and L-LTP performance during aging.

Disclosures: **W. Yang:** None. **X. Zhou:** None. **T. Ma:** None.

Poster

628. Learning and Memory: Aging III

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Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant AG16765

NIH grant DA08259

Title: Phosphorylated tyrosine 1472 NR2B levels are elevated in select synaptic compartments in the hippocampus of young and aging rats but only partially reduced by the presence of estrogen in aging rats

Authors: *T. A. MILNER[1,2], S. MAZID[2], M. DODOS[1], R. PURI[3], W. G. M. JANSSEN[3], J. H. MORRISON[3], B. S. MCEWEN[2], E. M. WATERS[2];
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Abstract: Estrogen modulation of synaptic plasticity in the adult rat hippocampus critically involves NMDA receptors. In the absence of estrogens, aging rats have lower NR2B subunit levels in the lateral portion of the active synaptic zone that are restored in the presence of estrogens (Adams et al. JCN 2004). This suggests that estrogens may impact the mobility of NMDA receptors across the synapse. Here, we examine whether phosphorylated tyrosine 1472 NR2B (pY1472), which is critically involved in the surface expression of NMDA receptors (Zhang et al., J. Neurosci. 2008), is altered in aged synapses in the absence and presence of estrogen. For this, young (2 mo old) and aged (~24 mo old) rats were ovariectomized (OVX) and treated with either 17β-estradiol or vehicle for 2 days and then dorsal hippocampus sections were embedded in plastic (same rats as used by Adams et al., 2004). Serial sections through the CA1 stratum radiatum were collected on formvar-coated slot grids (5-6/grid), labeled for pY1472

NR2B (Phosphosolutions) using immunogold and analyzed by electron microscopy. Overall, the number of pY1472 gold particles was greater in the pre- (terminals) and post-(spines) synaptic compartments of OVX vehicle-treated aged OVX rats compared to other groups. In aged rats, presynaptic pY1472 levels were elevated in regions containing the readily releasable and reserve pool of synaptic vesicles. Estradiol-treatment reduced the levels of pY1472 in both of these pools to levels seen in young rats. Postsynaptically, both young and aged OVX rats had high levels of pY1472 in the PSD and spine cytoplasm that were reduced similarly by estradiol. However, pY1472 levels in aged OVX rats were selectively elevated in the regions adjacent to the post-synaptic density and were not reduced by estradiol. Interpretation: NR2B endocytosis is blocked by phosphorylation at Y1472 and elevated pY1472 is detected during low estrogen states and with increased age. Because pY1472 is reduced by estradiol treatment, this suggests another mechanism through which estrogen promotes synaptic plasticity by facilitating endocytosis.

Disclosures: **T.A. Milner:** None. **S. Mazid:** None. **M. Dodos:** None. **R. Puri:** None. **W.G.M. Janssen:** None. **J.H. Morrison:** None. **B.S. McEwen:** None. **E.M. Waters:** None.

Poster

628. Learning and Memory: Aging III

Location: Hall A

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Topic: F.02. Animal Cognition and Behavior

Support: The Dana Foundation to ACP

Alzheimer's Drug Discovery Foundation #20120703 to ACP

NIH grant MH102065 to JDG

Title: The glutamate modulator riluzole alters hippocampal gene expression patterns associated with age-related cognitive decline

Authors: *J. KOGAN, J. D. GRAY, R. L. DAVIDSON, B. S. MCEWEN, A. C. PEREIRA; McEwen Lab., The Rockefeller Univ., New York, NY

Abstract: Decreased memory function with age often leads to poor quality of life in older adults. The neural circuits susceptible to aging are comprised of glutamatergic pyramidal neurons that furnish cortico-cortical connections between the association cortices as well as the excitatory hippocampal connections that subserve memory and cognition. Synaptic NMDA receptor activation is critical for learning and memory while extrasynaptic NMDA activity leads to long-

term depression and excitotoxicity. Riluzole is a glutamate modulator that increases glutamate-glutamine cycling and glutamate uptake, potentially increasing synaptic glutamatergic activity while preventing glutamate overflow to the extrasynaptic space. This drug has previously been shown to prevent age-related memory decline in rodents (Pereira et al PNAS 2014). This study seeks to evaluate the gene expression changes underlying this effect. Rats were given riluzole in the drinking water from 10 months to 14 months. Animals were sacrificed and the hippocampus was dissected out. RNA was extracted for sequencing on an Illumina Hi-Seq 2500 at a depth of 60 million reads. Differential expression analysis was conducted using Strand NGS software and gene lists were further analyzed for relevant Gene Ontology (GO) terms and pathway analysis using DAVID analysis tools. We found 233 genes significantly decreased in the riluzole group that were up-regulated with age and 95 genes showing the opposite pattern. GO analysis indicated that both these lists were enriched in genes associated with transmission of nerve impulse, synaptic transmission and ion transport. RNA was also used to create a cDNA library for qRT-PCR validation of these targets. A separate cohort of animals was tested for hippocampal-dependent memory using the Y-maze. These rats were subsequently perfused for immunohistochemical analysis. EAAT2 (Glt-1) is an astrocytic glutamate reuptake transporter and decreased levels of this gene are commonly associated with excitotoxicity. We observed a significant positive correlation between EAAT2 levels with riluzole treatment and y-maze performance, suggesting that riluzole may act to improve hippocampal function through regulation of the glutamatergic system. This study expands on previous work by revealing gene expression changes in the hippocampus that underlie the ability of riluzole to improve hippocampal memory in rodents. These gene patterns will allow us to gain a deeper understanding of the aging brain and potentially lead to development of novel drug targets for age-related cognitive decline and Alzheimer's disease.

Disclosures: **J. Kogan:** None. **J.D. Gray:** None. **R.L. Davidson:** None. **B.S. McEwen:** None. **A.C. Pereira:** None.

Poster

628. Learning and Memory: Aging III

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 628.14/BB1

Topic: F.02. Animal Cognition and Behavior

Support: Center for Alzheimer's Disease and Related Disorders at SIU School of Medicine

R01 AG019899

P01 AG31736

Title: Conserved memory and hippocampal glutamate in a growth hormone receptor knockout model of extended life span

Authors: *K. N. HASCUP[1], P. J. FITZGERALD[1], S. O. BRODERICK[1], S. RANDALL[1], J. J. KOPCHICK[4], A. BARTKE[2], E. R. HASCUP[3];
[1]Neurology, Ctr. for Alzheimer's Dis. and Related Disorders, [2]Intrnl. Med., [3]Neurology, Ctr. for Alzheimer's Dis. and Related Disorders, Pharmacol., Southern Illinois Univ. Sch. of Med., Springfield, IL; [4]Biomed. Sciences, Edison Biotech. Inst., Ohio Univ., Athens, OH

Abstract: Growth Hormone Receptor Knockout (GHR-KO) mice present with increased longevity (30-36 mos) and healthspan as compared to normal aging littermates. Previous studies indicate hippocampal mRNA levels for vesicular glutamate transporters remain constant in GHR-KO, but decrease with age in normal aging littermate controls (Hascup *et al*, 2015). Because of glutamate's involvement in learning and memory, we examined cognitive performance and *in vivo* hippocampal glutamate dynamics in 20-24 mos female GHR-KO and normal aging littermate controls. Spatial learning and memory was assessed with the Morris water maze (MWM). By the 5th training session, GHR-KO and littermate controls traveled a similar duration (23.4 ± 4.6 and 27.0 ± 8.8 s, respectively) and distance (4.3 ± 0.8 and 4.7 ± 1.7 m, respectively) to locate the submerged escape platform (both significantly ($p<0.001$) decreased compared to the 1st training session), indicating no differences in learning between genotypes. During the probe challenge, GHR-KO mice took a more efficient path (Fig 1A) and less time (12.7 ± 2.3 s; $p<0.05$) to first platform cross compared to control littermates (28.7 ± 7.1 s), supporting retention of reference memory in GHR-KO mice. One week following MWM, mice were isoflurane anesthetized and a glutamate selective microelectrode array coupled with *in vivo* electrochemistry was used to examine glutamatergic neurotransmission (basal, evoked release, and uptake) in the dentate gyrus (DG), CA3, and CA1. Basal and stimulus-evoked (70 mM KCl, isotonic, pH 7.4, ~150nl) glutamate was significantly attenuated in all hippocampal subregions of GHR-KO compared to littermate controls (Fig 1B & C). No differences in glutamate uptake were observed in any subregion. Increased basal CA3 glutamate negatively correlated with path efficiency to first platform cross during MWM probe (Fig 1D). These data support elevated basal and evoked-glutamate release observed in normal aging littermate controls impairs reference memory, which was not observed in the GHR-KO mouse model of increased healthspan.

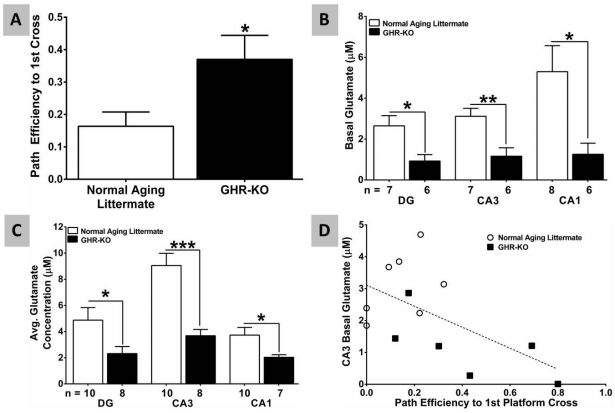

Figure 1: A) GHR-KO swam a more direct path to the first platform cross compared to normal aging littermates (n=10). B & C) Basal and stimulus-evoked glutamate release was elevated in all hippocampal subregions of normal aging mice. D) CA3 basal glutamate negatively correlates (Pearson r = -0.5741; p<0.05) to path efficiency. Figures A, B & C: Mean ± standard error; two-tailed t-test; *p<0.05, **p<0.01, ***p<0.001.

Disclosures: K.N. Hascup: None. **P.J. Fitzgerald:** None. **S.O. Broderick:** None. **S. Randall:** None. **J.J. Kopchick:** None. **A. Bartke:** None. **E.R. Hascup:** None.

Poster

628. Learning and Memory: Aging III

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 628.15/BB2

Topic: F.02. Animal Cognition and Behavior

Support: Center for Alzheimer's Disease and Related Disorders

Title: Hippocampal glutamate and cognition is altered in normal aging C57BL/6J mice

Authors: *S. O. BRODERICK[1,2], K. N. HASCUP[2], E. R. HASCUP[2,3];
[2]Dept. of Neurology, Ctr. for Alzhiemer's Dis. and Related Disorders, [3]Dept. of Pharmacol., [1]SIU Sch. of Med., Springfield, IL

Abstract: Aging is an important issue as population distributions and life expectancies are changing, resulting in increased older populations living longer than previous generations. Understanding the aging process in the brain can give insight into normal age-related cognitive decline as well as accelerated decline common in disease states, such as Alzheimer's disease. Our goal is to present a comprehensive view of how normal aging alters cognition and hippocampal glutamate (Glu) neurotransmission in male C57BL/6J mice. Mice were divided into 2-4, 6-8, or 12-15 month age groups (n = 10-13) and evaluated for learning and memory using Morris Water Maze (MWM). During MWM, subjects underwent five training days (learning)

followed by a single probe trial (memory). We observed an age-related decline in learning when examining path efficiency on the final training day, with 12-15 month mice exhibiting decreased cognition compared to 2-4 month mice (0.31 ± 0.03 and 0.45 ± 0.04, respectively; $p<0.05$). Similarly, memory impairments were evident when comparing platform entries corrected for distance traveled, which were elevated in 2-4 month old mice compared to the 12-15 month group (0.38 ± 0.05 and 0.21 ± 0.05 platform entries/m traveled, respectively; $p<0.05$) and 6-8 month group (0.23 ± 0.04 platform entries/m traveled; $p<0.05$). Following a recovery period, *in vivo* Glu neurotransmission was measured in CA1, CA3 and dentate gyrus (DG) regions of isoflurane anesthetized mice. A microelectrode array selective for Glu and micropipette with 70 mM KCl (isotonic, pH 7.4) was stereotaxically placed in the hippocampal subregion of interest. We observed a trend of decreasing stimulus evoked Glu release with age in the DG of 2-4 month, 6-8 month and 12-15 month C57BL/6J mice (3.8 ± 1.1 μM, 2.8 ± 0.5 μM, and 2.0 ± 0.3 μM, respectively). Furthermore, increased Glu release in the DG positively correlated with platform entries per distance traveled when examining the three age groups (Pearson $r = 0.48$, $p<0.05$). These results demonstrate that hippocampal Glu neurotransmission varies with age and may influence cognitive decline associated with normal aging. Future studies are planned to add 18-20 and 24+ month old groups to better understand the relationship between hippocampal function and cognition in advanced age.

Disclosures: S.O. Broderick: None. **K.N. Hascup:** None. **E.R. Hascup:** None.

Poster

628. Learning and Memory: Aging III

Location: Hall A

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Topic: F.02. Animal Cognition and Behavior

Support: CIHR (MOP 119454)

Fonds de recherche Québec-Santé

Title: A docosahexaenoic acid diet prevented cognitive decline in mice knock-in for human apolipoprotein e epsilon 4 allele

Authors: *M. PLOURDE[1], R. CHOUINARD-WATKINS[2], M. VANDAL[3], F. CALON[3]; [1]Res. Ctr. On Aging, Sherbrooke, QC, Canada; [2]Univ. de Sherbrooke, Sherbrooke, QC, Canada; [3]Univ. Laval, Québec, QC, Canada

Abstract: We previously showed that the metabolism of docosahexaenoic acid (DHA), an omega-3 fatty acid, is disrupted in humans and in transgenic mice carrying human apolipoprotein E epsilon 4 (APOE4) allele. Carrying APOE4 is recognized as being the most important genetic risk of developing Alzheimer's disease. Moreover, contrary to non-carriers of APOE4, carriers seem not protected against cognitive decline when consuming fatty fish. We have shown that brain DHA uptake is lower in APOE4 mice compared to APOE3 mice such that APOE4 mice might be more vulnerable to DHA deficiency, hence contributing to higher risk of developing cognitive decline. However, we have preliminary data in humans suggesting that with high doses of dietary DHA, its homeostasis can be rebalanced, hence potentially contributing to delay the onset of cognitive decline. The objective of this study was to evaluate whether dietary DHA intake prevent cognitive decline and whether proteins involved in neurotransmission are modified by the diet in APOE4 mice compared to APOE3 mice. To investigate this objective, four months old APOE3 (n = 32) and APOE4 (n = 38) mice were fed a control diet or a DHA diet for 8 months. At 12 months, animals were tested for visual and spatial memory using object recognition (OR) and Barnes maze (BM), respectively. A recognition index (RI) was calculated in the OR test whereas primary errors and escape latency were calculated in the learning phase of the BM. We also investigated by Western blot the following proteins in parieto-temporal cortex: SNAP25, synaptophysin, PSD95. Our results showed that APOE3 mice fed the control or the DHA diet recognised the new object whereas in APOE4 mice, only those fed the DHA diet recognised the new object. Escape latency was higher in APOE4 mice fed the control diet compared to APOE3 mice but there was no difference in escape latency between the genotypes when the mice were fed DHA. There was no difference in the synaptic protein levels in parieto-temporal cortex between genotypes and diets. These results support that DHA intake could be a nutritional strategy preventing cognitive decline in APOE4 carriers when provided at high doses. However, the mechanism behind this positive effect on cognition seems not related to synaptic protein content. Therefore, more investigations are needed to understand by which mechanism DHA intake prevented cognitive decline in APOE4 since these result could help designing therapeutic strategies for prevention of cognitive decline.

Disclosures: **M. Plourde:** None. **R. Chouinard-Watkins:** None. **M. Vandal:** None. **F. Calon:** None.

Poster

628. Learning and Memory: Aging III

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 628.17/BB4

Topic: F.02. Animal Cognition and Behavior

Support: Center for Nutrition, Learning and Memory

Title: Dietary supplementation with quercetin rejuvenates cognitive performance independent of adult hippocampal neurogenesis

Authors: *K. DU[1,2], S. D. PEREZ[1], P. T. KOZAK[1], A. A. SHERIFF[1], J. H. BAXTER[3], R. VAZHAPPILLY[3], J. S. RHODES[1];
[1]Beckman Inst. for Advanced Sci. and Technol., Univ. of Illinois At Urbana Champaign, Urbana, IL; [2]Div. of Nutritional Sci., Univ. of Illinois at Urbana Champaign, Urbana, IL; [3]Abbott Nutr., Columbus, OH

Abstract: Nutritional supplementation with quercetin, phosphatidylserine-docosahexaenoic acid (PS-DHA) compound, CDP-choline (citicoline), 5-methyltetrahydrofolic acid (Metafolin), and α-tocopherol have been suggested to ameliorate cognitive aging, but mechanisms are not known. The objective of this study was to measure the effect of these micronutrients on adult hippocampal neurogenesis and cognitive performance in a mouse model. Aged female and male C57BL/6J mice 18 months old were fed 8 different treatment diets for 4 months, before being tested on a battery of cognitive behavioral tasks. The 8 treatment diets (n=10 males and 10 females per group) were: 1) control (AIN93M), 2) 50% deficient in vitamins and minerals, 3) 150% elevated vitamins and minerals, 4) 0.051 g/kg quercetin, 5) 0.102 g/kg quercetin, 6) PS-DHA, 7) a combined supplement of CDP-choline, 5-MTHF, and α-tocopherol, and 8) a diet containing all mentioned supplements. Animals were euthanized at the end of the study to quantify numbers of new neurons by immunohistochemical detection of doublecortin (DCX). Young (2 months old) mice were also measured without dietary manipulation to serve as a reference for the aging-induced decline in the outcome measures. Quercetin significantly rejuvenated cognitive performance on the active avoidance learning and memory task, and the effect was enhanced when combined with the other micronutrients. No differences in number of DCX-positive cells were observed. Results confirm pro-cognitive effects of quercetin in an aging population, but mechanisms appear independent of adult hippocampal neurogenesis and remain unknown.

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Poster

628. Learning and Memory: Aging III

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 628.18/BB5

Topic: F.02. Animal Cognition and Behavior

Support: Center for Nutrition, Learning and Memory

Title: Dietary supplements with quercetin and micronutrients enhanced performance in active avoidance task in aged mice but no synergistic effect was found with voluntary wheel running

Authors: *P. PARK[1], T. K. BHATTACHARYA[1], C. RENDEIRO[1], B. D. PENCE[1], A. J. COBERT[1], J. L. RYTYCH[1], Y. SUN[1], K. W. KELLEY[1], R. W. JOHNSON[1], R. H. MCCUSKER[1], J. H. BAXTER[2], J. A. WOODS[1], J. S. RHODES[1];
[1]Univ. of Illinois At Urbana-Champaign, Urbana, IL; [2]Abbott Nutr., Columbus, OH

Abstract: Dietary supplements and physical exercise have been widely examined in regards to their beneficial effects on cognitive function in aging. In particular, quercetin, a flavonoid found in fruits and vegetables, has been shown to alleviate age-associated cognitive deficits, potentially through its ability to modulate synaptic plasticity and inflammation status. Earlier studies from our lab showed that when combined with other micronutrients (citicoline, 5-methyltetrahydrofolic acid, α-tocopherol and PS-DHA), chronic intake of quercetin significantly enhanced cognitive performance in aged C57BL/6J mice compared to the intake of quercetin alone. In the present study, we further investigated the synergistic effects of the quercetin and micronutrients with physical exercise on cognitive function. Aged male Balb/c mice were provided with running wheels for regular voluntary exercise and/or a diet containing quercetin for 4 months and were tested in active avoidance and social recognition tasks. Our preliminary data suggest that Balb/c mice fed with the quercetin-containing diet performed significantly better on the active avoidance task in comparison to the control aged group, whereas no synergistic effect with exercise was observed. Neither quercetin nor exercise showed improvements in social recognition task. Overall, these results indicate that a diet containing a combination of quercetin, citicoline, 5-methyltetrahydrofolic acid, α-tocopherol and PS-DHA is efficacious at ameliorating learning impairments in aging across different strains of mice. The precise mechanisms underlying such effects are not clear and will be further investigated.

Disclosures: P. Park: None. **T.K. Bhattacharya:** None. **C. Rendeiro:** None. **B.D. Pence:** None. **A.J. Cobert:** None. **J.L. Rytych:** None. **Y. Sun:** None. **K.W. Kelley:** None. **R.W. Johnson:** None. **R.H. McCusker:** None. **J.H. Baxter:** None. **J.A. Woods:** None. **J.S. Rhodes:** None.

Poster

628. Learning and Memory: Aging III

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Support: SAF2012-39852 Ministerio de Economia,Ciencia y Competitividat

FEDER founds

V.P is recipient of a Universidad de Guadalajara (Mexico) fellowship (V/2014/216).

Title: Cognition and behaviour impairment: is oxidative stress the earlier change commanding senescence? Lessons from senescence accelerated P8 mice

Authors: *M. PALLÀS[1], M. PUIGDORIOL-ILLAMOLA[2], V. PALOMERA-AVALOS[2], A. CAMINS[2], C. GRIÑÁN-FERRÉ[2];
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Abstract: Understanding of the magnitude and physiological significance of earlier oxidative processes on cognitive and behaviour changes and its relationship with aging processes or pathological settings is a frontier to be crossed in order to prevent/treat neurodegenerative disorders. Senescence-accelerated mice P8 (SAMP8), has been postulated as a biological tool to study pathological ageing. Behaviour changes, cognitive impairment and molecular and cellular changes linked to neurodegenerative diseases were characteristic in this mouse strain. Orchestrating these challenges, oxidative stress is one of the main actors in SAMP8 mice. Here we went deep on the temporary evolution of oxidative stress and its correlation with cognitive and behaviour changes, including molecular and cellular changes associated to neurodegenerative processes Oxidative stress disturbances namely 8-OHdG, 4-HNE, NF-kB, SOD1 levels are present as earlier as 1 month in SAMP8, but at this age cognitive impairment was not significant, although anxiety and temerosity were. Aged SAMP8 showed cognitive impairment, less oxidative stress but elevated levels of neurodegerative markers as Bax in reference to age-mated SAMR1. Accordingly with cognitive results changes in hallmarks of cognitive impairment as tau phosphorylation or neurogenesis process were found in aged SAMP8 mice in reference to age-mated SAMR1. Hyperphosphorylation of tau was significant higher in 9 months SAMP8 in front of SAMR1, but were equal at young age. In reference to neurogenesis process doublecortin (DCX) levels were significant decreased in young and old SAMP8, indicating a reduced capability to respond in front to a APP processing, an increase in BACE, sAPPbeta protein levels, concomitantly with a decrease in sAPPalfa, indicating a neurodegerative process likely Alzheimer's dementia in 9 months SAMP8 mice. The correlation among levels of oxidative levels and behavioural changes between SAMP8 and SAMR1 at the

different ages studied indicated that oxidative stress gives the pathway of molecular and cellular mechanisms that landing in cognitive impairment and neurodegeneration. Oxidative stress reduction is therefore a main and easily strategy to prevent neurodegenerative diseases.

Disclosures: **M. Pallàs:** None. **M. Puigdoriol-Illamola:** None. **V. Palomera-Avalos:** None. **A. Camins:** None. **C. Griñán-Ferré:** None.

Poster

628. Learning and Memory: Aging III

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FEDER founds

V.P is recipient of a Universidad de Guadalajara (Mexico) fellowship (V/2014/216).

Title: Epigenetic changes mediated by miRNAs as a cause of rapidly aging and cognitive impairments in female SAMP8 mouse model

Authors: *C. G. FERRE, JR[1], V. PALOMERA-AVALOS, Jr.[1], D. PUIGDORIOL-ILLAMOLA, Jr.[1], D. ORTUÑO-SAHAGÚN, Sr.[2], A. CAMINS, Sr.[1], M. PALLÀS, Sr.[1]; [1]Univ. of Barcelona, Barcelona, Spain; [2]Univ. de Guadalajara, Guadalajara, Mexico

Abstract: The role of epigenetics in the control of transcriptional mechanisms is one of the earliest emerging fields in senescence processes. These age-associated transcriptional signatures seem to be controlled by non-coding RNAs, known as microRNAs (miRNA). These miRNAs are small molecules (22 nucleotides approximately) that regulate gene expression by binding to their target messenger RNA (mRNA) inhibiting its translation, or, less frequently, promoting its degradation. One miRNA could potentially regulate large numbers of target genes synchronously, which implies that miRNAs may be important sculptors of transcriptional networks. As such, they are attractive candidates for regulating development and pathological changes. Thus, we chose the spontaneous senescence-accelerated P8 mouse model (SAMP8) which exhibit age-related deterioration in learning and memory abilities, and SAMR1 as a control to explore AD-associated pathogenesis and the links between miRNAs and AD. It is feasible that the differences among SAM strains could be explained through the link between these factors and epigenetic changes. For this reason, we focus on SAMP8 epigenetic alterations

through screening of the expression of 84 mature miRNAs in hippocampus of females SAMR1 and SAMP8 (1 and 9 months) by using the *miScript®.* These miRNAs were chosen because they are expressed differently during the progression of neurological diseases. The results of microarray analysis showed that the family of let-7, miR-26b-5p, miR-29a-3p, miR-29c-3p, miR-146a-5p, miR-151a-3p, miR-181a-5p miR-191-5p, miR-298, miR-485-5p were all expressed differently depending on the strain and age. The mirDB is an online database for miRNA target prediction and functional annotations and its analysis showed that these miRNAs are also implicated in cell fate determination, senescence, apoptosis, proliferation, stress and regulation of epigenetical enzymes and β-amyloid processing. Results were validates by quantitative real-time PCR. The data obtained pointed out several miRNAs that participated as regulators of aging and neurodegeneration in female SAMP8 mice. ACKNOWLEDGEMENTS: SAF2012-39852 "Ministerio de Educación y Ciencia". Spain. V.P is recipient of a Universidad de Guadalajara fellowship (Mexico).

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Poster

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European Regional Development Fund

Title: Reframing role of resveratrol in neurodegeneration: Oxidative stress, mitochondrial function and Wnt-pathway modulation in the brain of metabolically stressed SAMP8 mice

Authors: *V. PALOMERA[1], C. GRIÑÁN-FERRÉ, Jr[2], A. CAMINS[2], N. AMARO-UMBERT[2], M. PUIGDORIOL-ILLAMOLA[2], C. SANFELIU[3], A. M. CANUDAS[2], M. PALLÀS[2];
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Abstract: Alzheimer´s disease (AD) results in an irreversible loss of neurons, especially in the associative cortex and the hippocampus. Senescence-accelerated mouse prone 8 (SAMP8) has been proposed as a model for studying both the earliest neurodegenerative changes associated with AD as well as the progression of this disease, as it includes the age-related cognitive deficits and neuropathological abnormalities. Growing evidence indicates that mitochondrial dysfunction is a common feature of neurodegenerative diseases and is observed at an early stage in the pathogenesis of AD. On the other hand, the activation of the Wnt signaling pathway has an essential role in synaptic maintenance and neuronal function, and its deregulation has also been implicated in AD. We examined the effect of resveratrol in neurodegenerative processes, studying changes in oxidative stress, mitochondrial dysfunction and Wnt signaling induced by a high fat diet (HFD) as a metabolic stressor in 4-month-old mice. The results show an increase of (active) β-catenin on HFD-mice treated with resveratrol, target of Wnt pathway. Significant changes in the expression of Dickkopf, Dvl3, Axin1 LRP6 and GSK3 β were observed. Furthermore, the HFD caused a significant decrease in the expression of the OXPHOS complex, which was blocked in resveratrol-treated animals. Levels of mitochondrial fusion proteins OPA and Mitofusin2 were modified by HFD. Resveratrol blocked these differential protein expressions, pointing to a reduction in the fusion process. Furthermore, resveratrol reverted changes in oxidative stress markers. These results suggest than the Wnt pathway was modulated by resveratrol in SAMP8 mice; inhibition of Wnt renders in this model an increase in active β-catenin. Resveratrol's antioxidant properties were manifested by SOD increase and changes in oxidative stress and mitochondrial function markers. In conclusion, this study corroborates the importance of redox mechanisms in the neuroprotective effect of resveratrol, supporting the theory of the crucial role of oxidative stress in the shift from normal brain aging to pathological aging; moreover results support the hypothesis that this polyphenol may have a pleiotrophic effect on cellular processes, ranging from mitochondrial functioning to Wnt modulation.

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Poster

628. Learning and Memory: Aging III

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Topic: F.02. Animal Cognition and Behavior

Support: BU Research and Scholarship Grant

Title: The ability of concord grape juice to reverse a latent learning impairment during aging in rats depends on the duration of the supplement

Authors: *E. M. STOUFFER, P. N. MICHENER, L. C. WILSON;
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Abstract: Two experiments were conducted to examine the ability of Concord grape juice (CGJ) to reverse the latent learning impairment that normally begins during middle age in male rats. The purpose of Experiment 1 was to determine the minimum duration of the CGJ supplement necessary to reverse the latent learning impairment normally seen in middle-aged male rats, while Experiment 2 was conducted to determine if CGJ would also be able to reverse this impairment in older male rats. In Experiment 1, 40 middle-aged (11 months old) male Sprague-Dawley rats were given 25 ml of a 50% concentration of CGJ every other day for 1, 2, 3, or 4 weeks. All rats were then trained and tested on the Latent Cue Preference (LCP) task. During training trials of the LCP task, the water-replete rats sampled water (a neutral stimulus) in 1 compartment of the 3-compartment LCP box on 1 day, and then had no water in a second compartment of the LCP box the following day (1 training trial), for a total of 4 training trials over 8 days. All rats were then water-deprived prior to a compartment preference test, during which they were allowed to move freely among the compartments with the water removed. Latent learning is demonstrated during the preference test if rats spend more time in the compartment that previously contained the water (water-paired). Results of Experiment 1 showed that the 11-month-old rats given CGJ for either 3 or 4 weeks prior to the LCP task showed a significant preference for the water-paired compartment, indicating intact latent learning abilities. However, the 11-month-old rats given CGJ for only 1 or 2 weeks showed impaired latent learning (no compartment preferences). In Experiment 2, male Sprague-Dawley rats that were 14 months old (n = 10) were given CGJ every other day for 3 weeks, and male Sprague-Dawley rats that were 20 months old were given CGJ every other day for either 3 weeks (n = 9) or 8 weeks (n = 10). All rats were then trained and tested on the LCP task as described in Experiment 1. Results of Experiment 2 showed that the 14-month-old rats given CGJ for 3 weeks and the 20-month-old rats given CGJ for 8 weeks showed a significant preference for the water-paired compartment (intact latent learning). However, the 20-month-old rats given CGJ for 3 weeks showed no compartment preferences (impaired latent learning). These results appear to indicate that the antioxidant, anti-inflammatory, and neurogenesis effects of the flavonoids in CGJ only have to be present for a short period of time during middle age to be able to reverse the functional degeneration of the brain regions necessary for latent learning, but need to be present for a much longer period of time in older rats in order to reverse the degeneration.

Disclosures: E.M. Stouffer: None. **P.N. Michener:** None. **L.C. Wilson:** None.

Poster

628. Learning and Memory: Aging III

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VA Merit Review Grant (Quinn)

Title: Centella asiatica alters mitochondrial and antioxidant response pathways and improves neuronal health and cognitive function

Authors: *N. E. GRAY[1], C. J. HARRIS[1], J. A. ZWEIG[1], M. HUNTER[1], J. F. QUINN[1,2], A. SOUMYANATH[1];
[1]Oregon Hlth. and Sci. Univ., Portland, OR; [2]Neurol. and Parkinson's Dis. Res. Educ. and Clin. Care Ctr. (PADRECC), VA Portland Hlth. Care Syst., Portland, OR

Abstract: Introduction: *Centella asiatica* is a medicinal plant traditionally used to enhance cognition. The water extract of *Centella asiatica* (CAW) reverses -amyloid (A)-induced cognitive deficits in mice and prevents A toxicity *in vitro*. CAW also affect improves mitochondrial function and induces the expression mitochondrial and antioxidant response genes *in vitro* both in the presence and absence of A suggesting potential utility beyond Alzheimer's Disease. Here we explore the cognitive enhancing, mitochondrial and antioxidant effects of CAW in healthy aged mice and neurons isolated from these animals. **Methods:** Dendritic arborization, synaptic density and mitochondrial and antioxidant gene expression were evaluation in neurons from C57J/B6 mice. Additionally 2 and 20 month old C57J/B6 mice were treated with CAW in their drinking water for two weeks prior to Morris Water Maze (MWM) assessment of learning and memory. Brain expression of synaptic markers as well antioxidant and mitochondrial genes was evaluated. **Results:** CAW increased dendritic arborization and spine density in primary neurons and induced the expression of antioxidant and mitochondrial genes. CAW improved performance in the MWM in aged mice but did not show as robust an effect in young mice. Hippocampal, cortical and cerebellar expression of mitochondrial and antioxidant response genes was induced in both young and old CAW-treated animals. We also observed an increase in synaptic gene expression in both young and old CAW-treated mice in the hippocampus and cortex but not cerebellum. **Discussion:** CAW improves neuronal health and cognitive function in models of healthy aging. Histological studies are underway to determine whether the changes in arborization and spine density observed in isolated neurons also occur in the brains of CAW-treated animals. CAW also increased expression of mitochondrial and antioxidant response genes both in primary neurons as well as in the brains of treated animals. It remains to be seen whether these gene expression changes contribute directly to the

improvement in cognitive function and neuronal health. Metabolomic analyses of the brains of treated animals are ongoing to identify other pathways that may be involved in the mechanism of action of CAW.

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Poster

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Topic: F.02. Animal Cognition and Behavior

Support: P01 AG022550

RI6039 UNTHSC Faculty Seed grant

Title: Dietary curcumin and caloric restriction improve functional outcomes in late middle age and early senescent C57BL/6 male and female mice

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Abstract: Dietary curcumin and caloric restriction may ameliorate age-associated functional decline based on their anti-inflammatory and/or antioxidant actions. To determine whether or not combining these two interventions would result in additive or synergistic benefits, dietary curcumin and caloric restriction were tested for functional end points, either alone or in combination, in late middle age (MAG) (15 months) and early senescent (AG) (20 months) C57BL/6J male and female mice. Mice were assigned in groups to receive: (i) base diet ad libitum (AL), (ii) weight stable caloric restriction (CR), (iii) curcumin in the base diet (7200 mg/kg diet) (CURAL) or (iv) curcumin plus CR (CURCR). After 8 weeks of treatment, mice underwent a behavioral battery that tested for cognitive and psychomotor function. Cognitive flexibility was significantly better for MAG males CURAL compared to AL, but not under CURCR, suggesting an antagonistic interaction. On the other hand, MAG females under CR, CURAL and CURCR did significantly better than AL, suggesting that a negative interaction was not present in this sex. Curcumin alone (CUR) improved reversal performance in AG females, whereas CR was ineffective in the aged mice. None of the treatments led to significant

differences in the average path length for a water maze test of spatial memory, however, MAG CURCR males performed poorly in a probe test, further suggesting a negative interaction of these treatments in MAG males. There was no apparent effect of diet on spontaneous locomotion and rearing, although mice on CURCR and CR for both sexes and ages displayed improved performance in psychomotor tests of coordinated running, bridge walking and wire suspension. These results suggest that, when implemented separately, CR and CURAL have an ameliorative effect on impaired frontal cortical function present in late middle age. These effects were similar across different behavioral tasks and were non-interactive or antagonistic, suggesting that they could involve similar mechanisms. It is noteworthy that the combination treatment has a significant antagonistic effect on cognitive performance on MAG males but not females, and that both interventions alone and combined became less effective when implemented during early senescence when compared with middle age. Overall, the results indicate that curcumin intake mimics some of the beneficial effects of CR in the absence of diminished energy intake.

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Poster

629. Invertebrate Learning and Memory I

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Topic: F.02. Animal Cognition and Behavior

Support: BB/KO18515/1

WHRI Marie Curie COFUND

Title: Electrophysiological changes underlying lapses in memory consolidation

Authors: M. CROSSLEY, F. LORENZETTI, *P. R. BENJAMIN, M. O'SHEA, I. KEMENES; Univ. Sussex, Brighton, United Kingdom

Abstract: Memory consolidation is generally conceived as a process whereby new information sequentially moves to successively longer-term stores. In invertebrates and vertebrates, including humans, there are short periods of memory lapses during consolidation. Formerly these have been regarded simply as moments of vulnerability in memory formation. Our recent work on the snail Lymnaea however suggests that they are adaptive, allowing consolidation to be regulated so that acquisition and storage are effectively modified by new information after initial learning. Previously, we found that one-trial appetitive classical conditioning using sucrose as the

unconditioned stimulus (US) and gamma-nonalactone (GNL) as the conditioned stimulus (CS), was accompanied by memory lapses at 30 min and 2 hour after training. Memory consolidation was disrupted when a disturbance is applied to the animal during one of these lapse periods but not when presented at non-lapse times. Using intracellular recording techniques in an *in vitro* training paradigm we recorded changes in electrical activity after conditioning in key interneurons previously shown to be involved in the formation of memory in Lymnaea. Using the recently developed multielectrode array (MEA) technique we analysed more global network changes recorded from entire ganglia. Using these techniques, we were able to record conditioned responses to the CS during short-term memory (10 min after training) and intermediate-term memory (1 hour after training). At the 30 min lapse point no conditioned response was observed, consistent with earlier behavioral experiments. All the important types of buccal ganglion interneurons involved in feeding network activation (CV1) and motor pattern generation (N1M) followed this temporal pattern of responses. We also recorded an interneuron (PlB) that provided inhibitory modulation of the feeding circuit. This neuron was shown to reduce its spiking activity during memory expression. Using MEA we found novel types of neurons in CNS in ganglion areas not previously known to be involved in learning. One type followed the temporal sequence seen in buccal neurons but others showed responses to the US but not to the CS after training. By recording the feeding modulatory CGC interneurons we found that a tactile sensory disturbance applied during the lapse in memory blocked depolarization of the membrane potential when recorded at 24 hour after conditioning.

Disclosures: **M. Crossley:** None. **F. Lorenzetti:** None. **P.R. Benjamin:** None. **M. O'Shea:** None. **I. Kemenes:** None.

Poster

629. Invertebrate Learning and Memory I

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Topic: F.02. Animal Cognition and Behavior

Support: Medical Research Council

Title: The role of microRNAs in memory consolidation in Lymnaea

Authors: ***G. KEMENES**[1], D. VAVOULIS[2], S. KORNEEV[1];
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Abstract: After single-trial classical conditioning, there are well-defined time windows of activation of and requirement for key 'conventional' molecular players in the different phases of the consolidation of LTM in *Lymnaea*. Two important related discoveries we have made recently are: i) late LTM (24h post-training) requires transcription at 6h post-training, ii) at 6h post-training, there is ongoing phosphorylation of CREB1 and increased acetylation of H3, both of which can be measured in the 'learning ganglia' as well as in single identified neurons known to be involved in learning. However, the requirement for new protein synthesis for LTM only lasts for up to 1h after conditioning. Together, these findings gave rise to the testable hypothesis that newly transcribed non-coding RNAs (e.g., miRNAs) are involved in the early as well as intermediate-term phase of memory consolidation. In order to test this hypothesis we initiated studies of the temporal dynamics of the post-training expression of small non-coding RNAs (sncRNAs). sncRNA cDNA libraries were produced from the 'learning ganglia' dissected from experimental animals at 1h, 6h or 24h after a single conditioning trial, corresponding to the early, intermediate and late phases of memory consolidation. Next Generation Sequencing of the libraries and bioinformatic analysis revealed over a hundred individual sncRNAs with significant homology to miRNAs previously identified in other species, including *C. elegans, Drosophila, Aplysia*, mouse and humans. Notably, we identified individual annotated miRNAs belonging to 35 conserved miRNA families exhibiting learning-induced changes in their expression compared to naïve controls. Almost 50% of these differentially expressed miRNAs were found in all 3 experimental groups ('common' miRNAs). Interestingly, we identified 7 miRNAs that showed precisely timed changes in their expression. Among these 'phase-specific' miRNA families there are 5 that are specific for the 1h group and 2 that are specific for the 6h group. The rest of the miRNAs were differentially expressed in two phases and no miRNAs specific for the 24h group have been found. Many of the differentially expressed miRNAs are known to be involved in neuronal functions, including 14 that are also present in the human brain and 24 that are present in the *Aplysia* CNS. We have also identified potential targets for two of the differentially expressed miRNAs (*Lym-miR137* and *Lym-miR1175*) identified in our new experiments, Lym-CREB2-encoding mRNA and the long non-coding RNA *Lym-antiNOS3*. Notably, both molecules are important components of conventional mechanisms involved in memory formation.

Disclosures: G. Kemenes: None. **D. Vavoulis:** None. **S. Korneev:** None.

Poster

629. Invertebrate Learning and Memory I

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Topic: F.02. Animal Cognition and Behavior

Support: RSF grant 14-25-00072

Title: Activity of serotonergic neurons underlies choice between retrieval-induced extinction or reconsolidation of memory

Authors: *P. M. BALABAN, M. ROSHCHIN, A. ZUZINA, A. TIMOSHENKO, A. Y. MALYSHEV;
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Abstract: Retrieval of memory followed by reconsolidation can strengthen a memory, while retrieval followed by extinction results in a decrease of memory performance due to weakening of existing memory or formation of a competing memory. In our study we analyzed the behavior and responses of identified neurons involved in the network underlying aversive learning in terrestrial snail Helix, and made an attempt to describe the conditions in which the retrieval of memory leads either to extinction or reconsolidation. Using a specific for serotonergic neurons neurotoxin 5,7-DiHT it was shown previously that the serotonergic system is necessary for the learning, but is not necessary for maintenance and retrieval of the memory. These results suggest that serotonergic neurons that were shown to be necessary as part of reinforcement for developing the associative changes in the network may be not necessary for the retrieval of memory. The hypothesis tested in the present study is whether the activity of the "reinforcement" serotonergic neurons is the gate condition for the choice between extinction/reconsolidation triggered by the memory retrieval. It was shown in semi-intact and isolated CNS preparations that several serotonin applications effectively increased amplitude of synaptic inputs to the withdrawal interneurons, and that intracellular stimulation of a single identified giant serotonergic pedal cell #4 was effective as a reinforcement in Helix. We performed electrophysiological experiments in semi-intact preparations that allowed to deliver a drop of juice to the lip and simultaneously record intracellularly from interneurons involved in feeding and withdrawal behavior, and from the serotonergic "reinforcing" neurons. Recordings were made before and after associative training sessions in preparations. It was shown that after food-aversion training, the serotonergic cerebral interneurons involved in feeding have not changed significantly the responses to food, while the premotor interneurons (FMRFa-containing) involved in triggering the head and tentacle withdrawal started to respond with a spike discharge to previously subthreshold food stimuli. Serotonergic pedal neurons, whose intracellularly induced activity was shown to be capable to elicit associative changes in tentacle-withdrawal network, did not respond before training to the non-noxious stimuli. We examined the possibility that after associative training these neurons may start to respond during retrieval to previously ineffective stimuli, thus participating in triggering the reconsolidation.

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Poster

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Topic: F.02. Animal Cognition and Behavior

Support: NSF IOS-1051734

Title: Endovanilloid-mediated synaptic potentiation contributes to behavioral sensitization

Authors: *Y. WANG, B. D. BURRELL;
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Abstract: Transient Receptor Potential Vanilloid (TRPV) channels have established roles in sensory transduction, but also have an important neuromodulatory role in the central nervous system (CNS). In the CNS, TRPV channels can be activated by endocannabinoid/endovanilloid neurotransmitters, such as 2-arachidonoyl glycerol (2-AG) and anandamide (AEA), and can elicit long-term depression or persistent synaptic potentiation (the latter as a result of disinhibition). However, the functional/behavioral relevance of these opposing forms of endovanilloid-mediated neuromodulation is poorly understood. We have examined the patterns of activity that produced endovanilloid-mediated synaptic depression vs. potentiation and the behavioral effects of both forms of neuroplasticity using the well-characterized central nervous system of the medicinal leech. Low frequency stimulation (LFS) of non-nociceptive touch-sensitive neurons or bath-application of 2-AG produced TRPV-mediated depression of nociceptive (N cell) synaptic transmission as well as a decrease in the intensity of the defensive shortening reflex (Yuan & Burrell; J Neurophsiol 110: 2607). On the other hand, high frequency stimulation (HFS) of the N cell or 2-AG treatment elicited potentiation of non-nociceptive pressure (P) cell synaptic transmission and increased defensive shortening elicited by P cell activation. Pretreatment with the TRPV1 antagonist, SB 366791, could block 2-AG- and HFS-elicited potentiation of both behavior and synaptic transmission. Furthermore, pretreatment with 2-AG synthesis inhibitor, tetrahydrolipstatin (THL), also prevent HFS-induced synaptic and behavioral potentiation indicating that this activity-induced neuromodulation required 2-AG. Studies are currently underway to confirm that this endovanilloid-dependent modulation contributes to behavioral sensitization elicited by a more physiologically/behaviorally-relevant stimuli. These results indicate that endovanilloid-mediated synaptic potentiation plays an important role in behavioral sensitization. It is speculated that this endovanilloid-dependent neuromodulation may interact with serotonin-based forms of modulation that contribute to

sensitization given that 2-AG-mediated synaptic plasticity requires activation of 5HT2-like receptors (Yuan & Burrell 2012; Brain Res 1460:1). Sensitization is a fundamental form of behavioral modulation contributing to pain signaling, anxiety, addiction and learning and memory. Therefore, these findings provide significant insights into a previously unknown role for TRPV channels in this form of neurobehavioral plasticity.

Disclosures: Y. Wang: None. **B.D. Burrell:** None.

Poster

629. Invertebrate Learning and Memory I

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Topic: F.02. Animal Cognition and Behavior

Support: UNAM-DGAPA-PAPIIT-IN204014

Title: Effect of sleep deprivation on crayfish olfactory thresholds

Authors: J. SALAZAR-VÁSQUEZ[1], K. MENDOZA-ANGELES[1], G. ROLDAN[1], *J. HERNANDEZ-FALCON[2];
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Abstract: Under laboratory conditions, agonistic interactions in crayfish triads result in the formation of a hierarchy with a dominant animal, a submissive 1, and a submissive 2 animals. When agonistic interactions are carried out on a daily basis, the number and the intensity of these interactions are modified in such a way that positive contacts (threats, attacks and fights) diminish, while negative contacts (retreat and escape) increase. Previous results indicate that sleep deprivation induces an increase in the number of positive contacts. Olfactory information is the main sensory input in the establishment and maintenance of the dominance order. It has been proposed that during agonistic interactions a putative substance is released in the urine stream that animals discharge from the nephropores to the antennular area of its opponent, thus identifying them as a dominant or a submissive animal. Hence, the changes found in positive contacts of interacting sleep deprived animals, could be explained by modifications in its olfactory sensitivity. Therefore, the first objective of this study was to analyze the electrophysiological olfactory response of submissive animals to urine from the dominant one. Because sleep deprivation induces an increase in the intensity of agonistic encounters, a second objective of this work was to analyze the effects of sleep deprivation in the establishment and

maintenance of the hierarchical organization of crayfish triads and its effects on the electrophysiological olfactory response. We used male crayfish, Procambarus clarkii, in intermolt, and performed two types of experiments: A) Agonistic interactions in control and sleep deprived triads, and B) Analysis of the olfactory response to dominant and submissive urine, in control and sleep deprived crayfish. Our results indicate: (a) In sleep deprived triads positive contacts increase in intensity, amount, and duration. Negative contacts also increase, which seems to indicate a decrease in the sensitivity of animals to some kind of olfactory stimulus. (b) Olfactory stimulation of submissive crayfish using the dominant animal urine produced an escape reflex, whose latency was higher in sleep deprived crayfish. The larger latencies were found in the submissive crayfish 2. (c) Sleep deprivation reduced the brain and antennular electrical response to olfactory stimuli in dominant and submissive animals. These findings implicate that crayfish seem to detect each other through the olfactory input and that sleep deprivation increases the threshold for sensory stimuli.

Disclosures: J. Salazar-Vásquez: None. **K. Mendoza-Angeles:** None. **G. Roldan:** None. **J. Hernandez-Falcon:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 629.06/BB17

Topic: F.02. Animal Cognition and Behavior

Support: United States–Israel Binational Science Foundation (#2011466)

Israel Science Foundation (#1425-11)

European Commission EP-7 project STIFF-FLOP (#287728)

The Smith Family Laboratory at The Hebrew University

Title: Serotonin may convey positive and octopamine negative reinforcement signals to the learning network of Octopus vulgaris

Authors: T. SHOMRAT[1,2], *B. HOCHNER[1];
[1]Dept of Neurobiology, Hebrew Univ., Jerusalem, Israel; [2]The Ruppin Academic Center, Sch. of Marine Sci., Michmoret, Israel

Abstract: Octopuses uniquely combine vertebrate-like advanced behavior with a relatively simple invertebrate brain. This feature makes them an ideal preparation for comparative analysis of brain mechanisms evolved to mediate complex behaviors. The vertical lobe (VL), a pivotal brain region in the octopus learning system, has a robust activity-dependent long-term synaptic plasticity (LTP), analogous to suggested mechanisms for learning and memory in mammals. Serotonin (5-HT) is a facilitatory neuromodulator of synaptic transmission of the glutamatergic synaptic input to the VL, the same synaptic input that undergoes this LTP. However, differently from its related molluscan model, the *Aplysia* sensory-motor synapse, prolonged exposure to 5-HT does not lead to intermediate- or long-term potentiation. Yet, the short-term facilitatory effect of 5-HT leads to an indirect reinforcement of induction of the activity-dependent LTP. Here we show a similar short-term facilitatory effect for octopamine (OA). In contrast to 5-HT, which enhances induction of LTP by high frequency stimulation (HF-LTP), 100μM OA blocks induction of HF-LTP. Moreover, OA, when co-exposed with IBMX (increases intracellular cAMP and/or cGMP) depotentiates a previously induced HF-LTP. We therefore hypothesize that, during learning, 5-HT and OA serve as specific positive and negative reinforcement signals, respectively, allowing the octopus to associate a situation with its positive or negative consequences. Like results from mammals and insects, our research shows the universal importance of neuromodulators that, together with activity-dependent plasticity, determine the computational properties of learning and memory networks in animals with complex behavior.

Disclosures: **T. Shomrat:** None. **B. Hochner:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: F.02. Animal Cognition and Behavior

Support: United States–Israel Binational Science Foundation (#2011466)

Israel Science Foundation (1425-11)

Smith Family Laboratory at the Hebrew University

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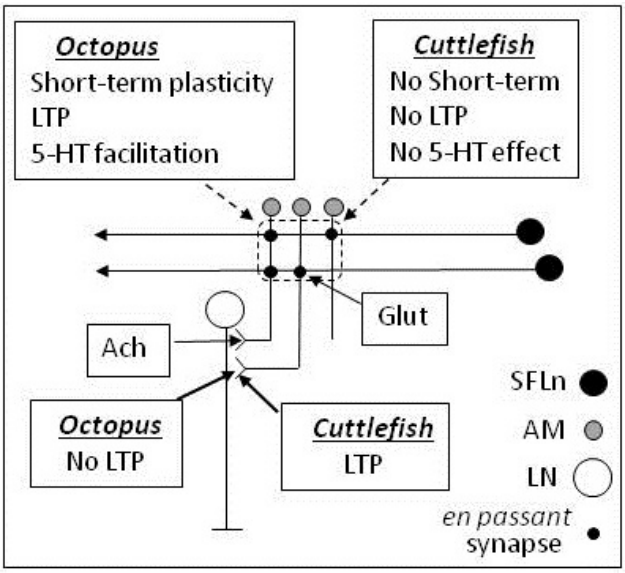
Title: Short- and long-term plasticity in homologous learning and memory networks of octopus and cuttlefish are highly variable in their molecular but not computational properties or connectivity

Authors: *A. TURCHETTI-MAIA[1], N. STERN-MENTCH[1,2], N. NESHER[1,2], B. HOCHNER[1], T. SHOMRAT[1,2];
[1]Dept. Neurobiology, Silberman Inst. of Life Sciences, The Hebrew Univ., Jerusalem, Israel;
[2]The Ruppin Academic Center, Sch. of Marine Sci., Michmoret, Israel

Abstract: The vertical lobes (VL) of *Octopus vulgaris* and *Sepia officinalis* mediate the advanced learning and memory of these cephalopod mollusks. In both animals the VL network comprises three neuron types organized in a fan-out fan-in connectivity (see scheme) where ~2 million superior frontal lobe neurons (SFLn) innervate tens of millions of amacrine interneurons (AM) in the VL. These AMs then converge onto only several thousand large efferent neurons (LN). The synaptic inputs to the AM are glutamatergic, while those to the LN are cholinergic. In contrast to the similarity in connectivity, short- and long-term plasticity and neuromodulation are dichotomically different in the two species (see scheme). The activity dependent LTP of the glutamatergic SFLn-AM synapses in the octopus is absent in the cuttlefish. Instead, the cuttlefish shows LTP of the cholinergic AM-LN synapses. However, theoretical considerations suggest that the two networks have similar computational properties (Shomrat *et al*. 2011). Here we compare the mechanisms mediating LTP. In octopus, nitric oxide synthase (NOS) inhibitors blocked LTP expression without affecting LTP induction, while in cuttlefish NOS inhibitors affected neither induction nor expression. Histochemical results support the physiological differences, as the octopus VL stained for NADPH-d (indicating NOS activity), while in cuttlefish only areas outside the VL were labeled. Preliminary results suggest that LTP induction in the octopus appears to be PKC- dependent, as phorbol-ester induced LTP and chelerythrine blocked LTP induction. In contrast, in cuttlefish, phorbol-ester induced either transient facilitation or had no effect. Also, the PKC inhibitors we have so far studied had inconsistent effects in cuttlefish. These results suggest that cephalopods are an unprecedented demonstration of profound variation among homologous networks. This suggests that evolutionary convergence or self organization may select among a variety of molecular mechanisms to construct cellular properties that are universal for learning and memory networks.



Disclosures: **A. Turchetti-Maia:** None. **N. Stern-Mentch:** None. **N. Nesher:** None. **B. Hochner:** None. **T. Shomrat:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 629.08/BB19

Topic: F.02. Animal Cognition and Behavior

Title: Inferring functional connectivity of neural circuits using information theoretic causality measures

Authors: ***Z. CAI**[1], B. AAZHANG[1], J. H. BYRNE[2];
[1]Electrical and Computer Engin., Rice Univ., Houston, TX; [2]Neurobio. and Anat., The Univ. of Texas Med. Sch. at Houston, Houston, TX

Abstract: Neural recording technologies such as voltage sensitive dyes (VSD) have enabled increasingly larger-scale simultaneous recording from neural networks, yet how signals recorded from individual neurons describe neural functions, plasticity and memory in a collective network is still poorly understood. In an attempt to tackle the aforementioned problem, we are applying and developing techniques to infer the underlying neural circuit by performing calculations of causal measures. Synthetic signals are generated by neural networks that are built using individual Hodgkin-Huxley neuronal models. Different estimation algorithms are compared and

implemented to extract the stochastic properties of the neural signals. Using these stochastic properties directed information (DI), a causal connectivity measure, is calculated between each pair of neurons. Together with the connectivity, other biophysical properties, such as the sign of a synaptic connection (i.e., excitatory or inhibitory) can also be inferred. Our initial results from using context tree weighting (CTW) estimation combined with DI show that this approach is able of detecting direct connections, eliminating indirect connections, and identifying the types of the synapses and their strength in small-scale realistic neural networks. Once the algorithm is validated using various artificial networks generated by the Hodgkin-Huxley conductance-based neural models, it will be applied to larger-scale real data. The buccal ganglion of *Aplysia* (see adjacent poster) will be used as a small brain test system. This method of combining large-scale recording techniques with signal processing tools to construct functional connectomes offers an automated tool to map a neural circuit and the ability to capture changes in synaptic strength due to learning or other behavioral modifications.

Disclosures: **Z. Cai:** None. **B. Aazhang:** None. **J.H. Byrne:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 629.09/BB20

Topic: F.02. Animal Cognition and Behavior

Support: Russell and Diana Hawkins Family Foundation Discovery Fellowship

Title: Voltage-sensitive dye (VSD) recordings reveal the network dynamics that underlie fictive behaviors

Authors: *C. NEVEU, D. A. BAXTER, J. H. BYRNE;
Neurobio. and Anat., The Univ. of Texas Med. Sch. At Houston, Houston, TX

Abstract: Feeding behavior in *Aplysia* is a useful model system for investigating the neural basis of behavior. Much of neural network that mediates feeding behavior is located in the buccal ganglia. Previous studies suggest that ~100 neurons in each hemi-ganglia are involved in the genesis of feeding behaviors such as the ingestion of food and the rejection of inedible objects. In isolated buccal ganglia preparations, at least two fictive behaviors (i.e., buccal motor patterns, BMPs) are observed: one is associated with ingestion (iBMPs) and another with rejection (rBMPs) of food. Both iBMPs and rBMPs have a protraction and retraction phase that correspond to different movements of a tongue like structure. Here, we report using a

combination of extracellular nerve recordings and VSD recordings of somatic action potentials to monitor activity in relatively large numbers of neurons within the feeding circuit. Extracellular recordings were used to categorize the BMPs as either iBMP or rBMP, and the VSD recordings monitored activity in up to 30 individual neurons simultaneously. Activity was monitored continuously for 2 min using the absorbance dye RH-155. Our preliminary results indicate that changes in activity occurred in at least half of the cells monitored via VSD recordings during spontaneous switching between fictive ingestion and rejection. Moreover, the majority of the changes in neuronal activity occurred during the protraction phase of BMPs. We also measured neuronal activity during an additional 2 min recording 5 min after the application of L-DOPA. Consistent with previous findings, L-DOPA increased the overall frequency of fictive behavior and biased the network towards iBMPs. Extensive reorganization of feeding circuit was observed in the presence of L-DOPA. For example, a comparison of neural activity during control iBMPs versus L-DOPA-induced iBMPs indicated that L-DOPA induced different levels of the activity in the majority of cells monitored via VSD recordings. Moreover, the preliminary data suggest that the neural activity during L-DOPA-induced iBMPs was substantially different from control iBMPs, which may reflect a fundamentally different mechanism for behavioral switching and/or genesis of fictive ingestion. Results from this study indicate that the use of VSD recordings will help to characterize the activity patterns of individual neurons during behavior and understand the extent to which a network of neurons can be reconfigured by prior events (e.g., learning) and extrinsic factors (e.g., pharmacological manipulations).

Disclosures: **C. Neveu:** None. **D.A. Baxter:** None. **J.H. Byrne:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 629.10/BB21

Topic: F.02. Animal Cognition and Behavior

Support: R01NS019895

R01NS073974

Title: Role of p38 MAPK and ERK activation in doxorubicin mediated attenuation of 5-HT-induced long-term synaptic facilitation

Authors: ***H. LAKSHMINARASIMHAN**, Y. ZHANG, L. J. CLEARY, J. H. BYRNE; Dept. of Neurobio. and Anat., The Univ. of Texas Med. Sch. At Houston,, Houston, TX

Abstract: Doxorubicin (DOX), a common chemotherapeutic agent, is associated with chemotherapy induced memory deficits colloquially known as “chemobrain.” In *Aplysia* sensory neurons, DOX (2.5 μM, 120 min) treatment results in elevated levels of phosphorylated ERK, phosphorylated p38 MAPK and phosphorylated CREB2, leading to an attenuation of 5-HT-induced LTF and enhancement of FMRFa-mediated LTD (Liu et al., J. Neurosci. 34:13289, 2014). The LTF impairment was rescued by inhibition of p38 MAPK. Given that ERK activation is essential for LTF and p38 MAPK activation is essential for LTD (Michael et al., Proc. Natl. Acad. Sci. 95:1864, 1998; Guan et al., J. Neurosci. 23:7317, 2003), the above results suggest that DOX activated p38 MAPK is more effective than activated ERK. The dominant effects of p38 MAPK may be due to differences in time-course or magnitude of activation. We tested this hypothesis by examining the temporal profile of ERK and p38 MAPK phosphorylation using varying durations of DOX treatments (2.5 μM for 30, 60, 90 and 120 min). The duration of DOX treatment significantly affected the activation of p38 MAPK (treatment x duration; $F(3,46) = 4.75$; $p = 0.006$) with significant main effect of DOX treatment (treatment; $F(1,46) = 32.08$; $p = 0.0$) as well as duration of DOX treatment (duration; $F(3,46) = 27.3$; $p = 0.0$). Peak p38 MAPK activation was observed after at least 90 min (increase by 32.4% at 30 min, 88.1% at 60 min, 93.3% at 90 min and 64.4% at 120 min compared to Vehicle) of DOX treatment. This result suggests that levels of active p38 MAPK increase with the duration of treatment. However, the DOX-induced increase in ERK activation (treatment; $F(1,54) = 7.1$; $p = 0.01$ and duration; $F(3,54) = 4.4$; $p = 0.007$) was relatively independent of the treatment duration (treatment x duration; $F(3,54) = 0.13$; $p = 0.93$) indicating that the increase in ERK activation is rapid (increase by 34.7% at 30 min, 20.6% at 60 min, 39.6% at 90 min and 33.5% at 120 min compared to Vehicle). These results suggest that over time the magnitude of the increase in active p38 MAPK dominates over the effects of activated ERK, resulting in attenuation of LTF and enhancement of LTD. We are now examining the effects of DOX pre-treatment (30 min) on the 5-HT-mediated changes in the activation of ERK and p38 MAPK. At this early time point, we aim to explore the nature of the interaction (additive versus synergistic) between DOX and 5-HT treatments on these kinases. We are also incorporating these findings into a computational model of the molecular mechanisms underlying LTF induction (Liu et al., J. Neurosci. 33: 6944, 2013) to design a training protocol to rescue the DOX-induced deficit of LTF.

Disclosures: H. Lakshminarasimhan: None. **Y. Zhang:** None. **L.J. Cleary:** None. **J.H. Byrne:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 629.11/BB22

Topic: F.02. Animal Cognition and Behavior

Support: NIMH RO1 MH 041083

NIMH F31 MH 100889

Title: The role of growth factor signaling in post-transcriptional RNA regulation during long-term memory formation in *Aplysia*

Authors: *A. M. KOPEC, A. A. MIRISIS, T. J. CAREW;
Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: It is widely appreciated that signaling via several different growth factor (GF) families is required for long-term memory (LTM) formation, but the roles of distinct GF families in mediating unique molecular and cellular signaling events remains to be elucidated. Previous data from our laboratory show that GF signaling via the TrkB and TGFβr-II receptors is engaged in unique spatial and temporal profiles during Two-Trial LTM formation in *Aplysia* (Kopec et al. 2015) Interestingly, these different GF families each mediate a unique phase of MAPK activation, but synergistically interact to regulate expression levels of the immediate early gene c/ebp. Specifically, Trial 1 TrkB signaling increases the expression of c/ebp, and Trial 2 TGFβr-II signaling prolongs the expression of this c/ebp message. To explore the mechanism by which Trial 2 TGFβr-II signaling prolongs the expression of c/ebp mRNA, we sought to characterize the level of c/ebp associated with the RNA binding protein ELAV, a member of the Hu family of RNA binding proteins which has been demonstrated to stabilize c/ebp transcripts in *Aplysia* (paper). Here we report that mRNA and protein levels of ELAV do not change from baseline 15 mins after Trial 2. However, RNA immunoprecipitation experiments demonstrate a positive correlation between the level of c/ebp induction after Trial 2 and the amount of c/ebp bound to ELAV. Collectively these data support the hypothesis that Trial 2 promotes the binding of ELAV and c/ebp mRNAs, and thus implicates the complex regulatory mechanisms of mRNA expression in LTM formation. In our next experiments, we will (i) test the hypothesis that ELAV-c/ebp binding induced by Trial 2 requires TGFβr-II signaling, (ii) further characterize the molecular signaling pathways that regulate ELAV-c/ebp associations, and (iii) determine the behavioral relevance of this association during memory formation in *Aplysia*, with the ultimate goal of examining post-transcriptional processing as an additional level of regulation important for plasticity and memory formation.

Disclosures: A.M. Kopec: None. **A.A. Mirisis:** None. **T.J. Carew:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 629.12/BB23

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant RO1 MH 041083

Title: Synaptic generation of a retrograde intracellular signal requires tyrosine kinase and mitogen-activated protein kinase activity in *Aplysia*

Authors: *S. STOUGH[1], A. KOPEC[2], T. CAREW[2];
[1]Psychology, Augustana Col., Rock Island, IL; [2]Ctr. for Neural Sci., New York Univ., New York, NY

Abstract: Cellular changes underlying memory formation can be generated in an activity-dependent manner at specific subsets of synapses. Thus an important question concerns the mechanisms by which synaptic signals communicate with the cell body in order to coordinate these cellular changes. The monosynaptic neural circuit underlying memory for sensitization in *Aplysia* is well-suited to study this question because different subcellular compartments (e.g. sensorimotor SN◊MN synapses, SN◊MN axonal connections, and SN cell bodies) can be manipulated and studied independently. We have previously shown that incubation of the SN◊MN circuit with a 5 min pulse of a high KCl (370mM) and serotonin (5HT, 50μM) , which combines depolarization with neuromodulation (activity-dependent [AD] stimulation), induces both MAPK activation in SN cell bodies and synaptic facilitation (Shobe et al., 2009). Here, we report that AD stimulation applied to the entire neural circuit activates MAPK in a temporally specific pattern in different subcellular compartments. Interestingly, we find that this temporal pattern of MAPK activation can be generated if the AD (KCl/5HT) training pulse is delivered only to the SN◊MN synapses in a split bath preparation (Sherff and Carew, 1999). Specifically, we find that (i) MAPK activation is first transiently generated at SN◊MN synapses during training, (ii) immediately after training MAPK is transiently activated in SN◊MN axonal connections and persistently activated in SN cell bodies, and finally, (iii) MAPK is activated in SN cell bodies and SN◊MN synapses 1hr after training. These data suggest there is an intracellularly transported retrograde signal generated at the synapse which is later responsible for delayed MAPK activation at SN cell bodies. This retrograde signal requires activation of a tyrosine kinase (TK) signaling cascade in the synapses at the time of training, but does not require TK signaling at SN cell bodies for 1 hr MAPK activation in SN cell bodies. An intriguing hypothesis is that MAPK, which is rapidly activated locally at the synapse in response to AD training, is itself the retrograde signal that travels to SN cell bodies. In support of this hypothesis, blocking MEK activity at the synapse disrupts subsequent persistent MAPK activation in SN cell bodies. In conclusion, we have identified a temporally and spatially coordinated profile of

MAPK activation following a synaptically-generated signal which could be a candidate mechanism that underlies communication between the synapse and cell body during memory formation.

Disclosures: S. Stough: None. **A. Kopec:** None. **T. Carew:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 629.13/BB24

Topic: F.02. Animal Cognition and Behavior

Support: NIH R25 NS 080686

NIMH RO1 MH 041083

Title: Non-nuclear ERK/MAPK signaling is temporally correlated with the opening of training windows for long-term memory formation in *Aplysia*

Authors: *A. CHEN, T. J. CAREW, G. T. PHILIPS;
New York Univ., New York, NY

Abstract: A highly conserved principle of learning and memory is that the temporal patterning of experiences regulates the acquisition and retention of long-term memory (LTM). We have previously shown that ERK/MAPK signaling plays an important role in supporting the interactions of spaced experiences during two-trial learning and LTM formation in *Aplysia* californica (Philips et al. 2013). Specifically, nuclear MAPK signaling, which was required for activation of CREB-mediated transcription, was temporally correlated with the opening of a permissive training "window" at 45min (but not at 15min or 1h) following training trial 1. Although Trial 1-induced MAPK signaling to CREB was shown to be necessary to support two-trial LTM formation, it remains unclear whether this signaling is responsible for opening permissive training "windows" for LTM formation. In the present study we show that MAPK is activated as soon as 30min after training trial 1, but no earlier (i.e. no activation is observed at 20min). Using immunohistochemistry we found that the activated MAPK is cytoplasmic (non-nuclear) at 30min, with significant nuclear translocation of MAPK occurring at 45min. Intriguingly, the CREB kinase p90rsk, which is localized to the cytoplasm and is an established target of trial 1 MAPK signaling, is significantly activated (phosphorylated at ser380) by 30min. Moreover, the non-nuclear MAPK signaling to p90rsk is temporally correlated with the opening

of the two-trial learning window: animals acquired and expressed LTM for sensitization with two-trial training at 30min, but not 20min training intervals. Thus, our data suggest that cytoplasmic ERK/MAPK activation engages the CREB kinase p90rsk to contribute to the "opening" of a permissive training window for LTM formation.

Disclosures: A. Chen: None. **T.J. Carew:** None. **G.T. Philips:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 629.14/BB25

Topic: F.02. Animal Cognition and Behavior

Support: NIMH 5T32 MH019524 to AA

NIMH T32 MH 963314 to AA

NIMH RO1 MH 041083 to TJC

Title: Molecular and cellular mechanisms of endogenous neurotrophic factor signaling during long-term synaptic plasticity in *Aplysia* californica

Authors: *A. ALEXANDRESCU[1], T. J. CAREW[2];
[2]Ctr. for Neural Sci., [1]New York Univ., New York, NY

Abstract: The molecular and cellular mechanisms of long-term memory formation are highly conserved across species. One such evolutionarily conserved mechanism is neurotrophic factor signaling. The marine mollusk *Aplysia* californica is a powerful model system for studying the molecular mechanisms of long-term synaptic plasticity underlying long-term memory for sensitization. Previous studies from our laboratory have shown that neurotrophic factor signaling critically participates in the formation of long-term synaptic facilitation and long-term memory (Purcell et al. 2003; Sharma et al. 2006; Kopec et al. 2015). Furthermore, we have identified a novel endogenous neurotrophic factor, *Aplysia* cysteine-rich neurotrophic factor (ApCRNF), which shares structural and functional characteristics with mammalian neurotrophins (Pu et al. 2014). When paired with subthreshold training for sensitization (1 tail nerve shock / 1 pulse of serotonin), exogenous application of recombinant ApCRNF induces a gain-of-function in both ERK/MAPK activation in sensory neuron somas and in long-term facilitation of sensory-motor neuron synapses. Using an immunocytochemical analysis, we find that ApCRNF protein is localized to the cytoplasm of both sensory and motor neurons. Furthermore, ApCRNF binds to

receptors on the cell surface of both sensory and motor neurons in co-cultures treated with exogenous recombinant ApCRNF. Our current studies are focused on an investigation of the molecular and cellular mechanisms engaged by ApCRNF within the sensory-motor neuron microcircuit during long-term synaptic facilitation.

Disclosures: A. Alexandrescu: None. **T.J. Carew:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 629.15/BB26

Topic: F.02. Animal Cognition and Behavior

Support: HHMI

NIH grant NS083690

Title: *Aplysia* neurotrophin acts as a presynaptic autocrine, anterograde, and retrograde signal during the transition from short-term facilitation to intermediate-term facilitation produced by 5HT at *Aplysia* sensory-motor neuron synapses

Authors: *I. JIN[1], H. UDO[2], E. R. KANDEL[1], R. D. HAWKINS[1];
[1]Dept. of Neurosci., Columbia Univ., New York, NY; [2]Dept. of Biol., Kyushu Univ., Fukuoka, Japan

Abstract: Spontaneous neurotransmitter release from the presynaptic neuron acts as an anterograde signal during the transition from short-term facilitation (STF) to intermediate-term facilitation (ITF) produced by 5HT at *Aplysia* sensory-motor neuron synapses (Jin et al., 2012a, b). It activates mGluR5 to recruits postsynaptic mechanisms of ITF, which may be an early step in a cascade leading to long-term facilitation (LTF) and synaptic growth. In addition, activation of presynaptic PKA during STF increases the release of *Aplysia* neurotrophin (ApNT) from the presynaptic neuron. The ApNT then binds to its receptor (ApTrk) on the presynaptic neuron and activates downstream signaling including PKA. This signaling cascade forms a presynaptic positive feedback loop that enhances spontaneous glutamate release and may also enhance presynaptic PKA for the transition to LTF (Jin et al., 2014). We report here that ApNT also acts as an anterograde signal in a transynaptic feedback loop. 10 min bath application of 5HT increases the release of overexpressed ApNT-pHluorin from the presynaptic neuron. Injection of antisense oligo against ApTrk into the postsynaptic motor neuron reduces the increase in mini

frequency produced by 10 min 5HT, and activation of postsynaptic ApTrk increases mini frequency. These data suggest that ApNT released from the presynaptic neuron activates postsynaptic ApTrk, which stimulates a retrograde signal that enhances presynaptic spontaneous release. Interestingly, ApNT also acts as the retrograde signal. Injection of siRNAi against ApNT into the postsynaptic neuron reduces the increase in mini frequency produced by 10 min 5HT, suggesting that postsynaptic ApNT is involved. Activation of postsynaptic ApTrk increases the release of overexpressed ApNT-pHluorin from the postsynaptic neuron. Furthermore, the increase in mini frequency produced by postsynaptic ApTrk activation is reduced by injection of antisense oligo against ApTrk into the presynaptic neuron. These results suggest that ApNT released from the postsynaptic neuron acts as a retrograde signal and enhances spontaneous transmitter release through activation of presynaptic ApTrk. In summary, ApNT plays three essential roles during the transition from STF to ITF produced by 5HT at *Aplysia* sensory-motor synapses: (1) it is part of a presynaptic positive feedback loop, which amplifies the signaling molecules required, (2) it acts as an anterograde signal to recruit postsynaptic mechanisms including ApNT itself, which then (3) acts as a retrograde signal, forming a transynaptic feedback loop that may also amplify the molecules required and coordinate the pre- and postsynaptic neurons.

Disclosures: I. Jin: None. **H. Udo:** None. **E.R. Kandel:** None. **R.D. Hawkins:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 629.16/BB27

Topic: F.02. Animal Cognition and Behavior

Support: NIH grant SC3GM111188

Title: Role of the nitric oxide signaling cascade in the induction of the behavioral changes produced by aversive stimuli in *Aplysia*

Authors: J. FARRUGGELLA, J. A. ACEBO, *M. L. WAINWRIGHT, R. MOZZACHIODI; Texas A&M Univ. - Corpus Christi, Corpus Christi, TX

Abstract: When *Aplysia* is exposed to aversive stimuli (i.e., electric shocks to the body wall), it exhibits a learned behavioral change known as sensitization through which defensive responses (e.g., the tail-siphon withdrawal reflex; TSWR) are enhanced. Training protocols that induce sensitization also cause a concurrent suppression of a non-defensive behavior, feeding.

Specifically, long-term sensitization (LTS) training (four 10-s trains of electric shocks spaced 30 min) induces sensitization and feeding suppression lasting at least 24 h, whereas single-trial sensitization (STS) training (one 10-s train of electric shocks) induces sensitization and feeding suppression lasting for at least 2 h but less than 24 h. Although serotonin has been shown to mediate sensitization, it is not involved in the concomitant suppression of feeding, suggesting that distinct signaling cascades regulate the different behavioral changes produced by aversive stimuli. This study sought to investigate whether nitric oxide (NO) contributes to the induction of sensitization and feeding suppression. Because the NO signaling cascade may contribute selectively to specific temporal domains of the changes produced by sensitizing stimuli, both LTS and STS training protocols were used. The NO synthase inhibitor L-NAME was used to block the NO signaling cascade. In all the experiments, L-NAME was injected systemically 1 h before training. TSWR duration and feeding (i.e., number of bites in a food extract solution) were assessed prior to and 24 h after LTS training, and 15 min and 2 h after STS training. For both training protocols, four groups were included: L-NAME-injected trained, L-NAME-injected untrained, vehicle-injected trained, and vehicle-injected untrained. Following the LTS protocol, sensitization and feeding suppression were blocked at the 24-h time point in L-NAME-injected trained animals, whereas they were both observed in vehicle-injected trained animals. Similarly, following the STS protocol, feeding suppression was prevented in L-NAME-injected trained animals at both 15-min and 2-h time points, whereas it was induced in vehicle-injected trained animals. Ongoing experiments are characterizing the contribution of the NO pathway to the sensitization induced by the STS protocol. The above findings suggest that the NO signaling cascade may contribute to the induction of both short-term and long-term feeding suppression. Interestingly, this signaling cascade also appears being involved in the induction of long-term sensitization, suggesting that a complex interaction between serotonin and NO pathways underlie the long-term changes induced by LTS training.

Disclosures: **J. Farruggella:** None. **J.A. Acebo:** None. **M.L. Wainwright:** None. **R. Mozzachiodi:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 629.17/BB28

Topic: F.02. Animal Cognition and Behavior

Support: Anticipated support from 1R15MH107892-01

Title: Persistent transcriptional correlates of long-term sensitization training in Aplyisa californica

Authors: J. PATEL[1], C. CONTE[1], S. HERDEGEN[1], S. KAMAL[1], I. E. CALIN-JAGEMAN[1], *R. CALIN-JAGEMAN[2];
[1]Biol., [2]Psychology, Dominican Univ., River Forest, IL

Abstract: Sensitization is a ubiquitous form of non-associative memory. The long-term expression of sensitization memory depends in part on persistent changes in gene expression. We are using microarray and qPCR to enumerate the persistent transcriptional changes accompanying long-term sensitization of the tail-elicited siphon-withdrawal reflex in the marine mollusc *Aplysia* californica. To accomplish this, animals receive unilateral long-term sensitization training. After behavioral confirmation of long-term memory 1 day after training, pleural ganglia are harvested, and gene expression is compared from the trained to untrained ganglia. We have so far confirmed or identified 7 transcripts that are strongly up-regulated for at least 24 hours after sensitization training: BiP, Tolloid/BMP-1, sensorin, Egr, GlyT2, VPS36, and an uncharacterized protein (LOC101862095). We are now in the process of conducting microarray analysis on pleural ganglia samples harvested 1 day after training to reveal the complete transcriptional profile accompanying long-term memory expression. This work will help shed light on the transcriptional networks that help sustain the expression of a long-term memory.

Disclosures: J. Patel: None. **C. Conte:** None. **S. Herdegen:** None. **S. Kamal:** None. **I.E. Calin-Jageman:** None. **R. Calin-Jageman:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 629.18/BB29

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant GM097502

Title: Classical conditioning in the *Aplysia* siphon-withdrawal preparation involves RNA synthesis and DNA methylation

Authors: *R. D. HAWKINS[1,2], I. ANTONOV[1], A. NAGARAJ[1], Q. YANG[1];
[1]Neurosci., Columbia Univ., New York, NY; [2]New York State Psychiatric Inst., New York, NY

Abstract: We have been studying mechanisms of simple forms of learning using a reduced preparation of the *Aplysia* siphon withdrawal reflex in which it is possible to record the activity and synaptic connections of identified neurons during the learning. The preparation undergoes intermediate-term habituation, dishabituation, sensitization, and classical conditioning that are similar to learning in the intact animal. Each of those forms of learning is due in part to plasticity at the synapses from LE sensory neurons to LFS motor neurons (Antonov et al., 1999, 2001, 2010). Conditioning involves pairing-specific facilitation at those synapses, which is due to two mechanisms that interact through retrograde signaling: (1) activity-dependent enhancement of the presynaptic PKA pathway and (2) Hebbian potentiation induced by activation of postsynaptic NMDA receptors (Antonov et al., 2003). The conditioning also involves NO, which comes from the L29 interneurons and acts directly in both the LE and LFS neurons (Antonov et al., 2007), where it activates HCN channels that enhance the NMDA current (Hawkins et al., 2014). We have now begun to examine mechanisms of long-term conditioning. In preliminary experiments the preparation exhibited 24 hr retention of the pairing-specific increases in siphon withdrawal and its correlates in the LE and LFS neurons, suggesting that long-term conditioning involves the same cellular mechanisms as intermediate-term conditioning. Conditioning was also accompanied by an increase in synaptophysin puncta, which may be an initial step in synaptic growth. In addition, we have begun to examine the role of gene regulation. We compared changes in the withdrawal reflex in groups that received either paired or unpaired training with a siphon tap CS and a tail shock US while the ganglion was bathed in either normal seawater or DMSO (control), the RNA synthesis inhibitors Actinomycin D or DRB, or the DNA methyl transferase inhibitor RG108. In the control group, paired training produced an increase in the response to the CS compared to either the pretest or unpaired training, demonstrating classical conditioning. Either Actinomycin D (50 μg/ml), DRB (300 μM), or RG108 (200 μM) significantly reduced conditioning during the later part of training. As controls, the drugs had no significant effects on unpaired training or the amplitude of the initial siphon withdrawal in response to either the CS or US. These results suggest that classical conditioning in this preparation involves DNA methylation and changes in transcription. An accompanying abstract (Bostwick et al, 2015) uses nRNAseq to identify transcripts preferentially expressed during the conditioning.

Disclosures: **R.D. Hawkins:** None. **I. Antonov:** None. **A. Nagaraj:** None. **Q. Yang:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 629.19/BB30

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant NS088835

Title: Impact of chronic sleep deprivation on short-term and long-term associative memory in *Aplysia* californica

Authors: *H. KRISHNAN, E. NOAKES, L. C. LYONS;
Biol. Science, Program in Neurosci., Florida State Univ., Tallahassee, FL

Abstract: Sleep is an evolutionarily conserved process and plays an important role in the modulation of memory. Chronic sleep restriction, prevalent in modern society, leads to cognitive deficits and performance impairments; however, the underlying mechanisms are not clear. Given the high degree of conservation underlying memory formation across species, the marine mollusk *Aplysia californica* with its relatively simple neural circuitry provides an ideal model for studying the interactions between sleep and memory formation. Previously, we have shown that *Aplysia* sleep in consolidated bouts, have higher arousal thresholds with longer response latencies during sleep, and demonstrate rebound sleep after sleep deprivation (Vorster et al., 2014). Using an associative learning paradigm, learning that food is inedible (LFI), in which the animal associates a specific netted seaweed with the failure to swallow, we previously found that 9 hours of acute sleep deprivation was sufficient to block the induction of short-term (STM) and long-term memory (LTM). We also found that 6 h acute sleep deprivation during the last half of the night blocked induction of LTM, but had no effect on STM. In our current research, we investigated the effects of chronic sleep restriction on short-term and long-term memory. In initial studies, we found that 3 consecutive nights of sleep deprivation during the last 4 h of the night blocked the induction of STM but not LTM. We are also examining the effects of more severe chronic sleep restriction on STM and LTM. Defining the interactions between sleep and memory through behavioral studies in a relatively simple model system provides a basis for future studies delineating the underlying mechanisms through which sleep affects memory and potentially will identify novel ways to alleviate cognitive deficits incurred due to restricted sleep.

Disclosures: H. Krishnan: None. **E. Noakes:** None. **L.C. Lyons:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 629.20/BB31

Topic: F.02. Animal Cognition and Behavior

Support: NIH R01 MH 55880

Title: The role of stimulus novelty in attention in the invertebrate *Aplysia*

Authors: K. PEARCE, M. E. KIMBROUGH, X. ZHAO, T. S. DEHGHANI, E. J. MOC, D. ENAYATI, S. S. BENTLEY, V. KONG, *T. W. ABRAMS;
Pharmacol., Univ. of Maryland Med. Sch., Baltimore, MD

Abstract: We recently explored whether the non-visual invertebrate *Aplysia* exhibits attention using a distraction paradigm. In general, distraction requires that a subject is first "paying attention" to a stimulus. We tested whether *Aplysia* could be distracted from a conditioned stimulus (CS) that animals had learned signaled the occurrence of a noxious US. Animals were first trained in a fear conditioning paradigm (Walters et al. 1981) with dilute carrot juice as the CS and tail shock as the US. The 90 s CS and the 15 s US coterminated during each of 6 pairing trials over 2 days. Sensitized animals received the same two stimuli during training, separated by 15 min. When the siphon withdrawal response (SWR) was tested in the presence of the CS on day 3, fear conditioned animals showed a substantially greater increase in the duration of the withdrawal response than sensitized animals. To test for the effect of a distractor, in posttests a very mild vibration stimulus was introduced 5 s prior to the onset of the CS. These weak distractor stimuli had no effect on the SWR of sensitized animals. In contrast, the presence of the distractor dramatically reduced or completely eliminated the enhanced SWR of fear conditioned animals. This suggests that in *Aplysia*, the fear response to the CS requires that animals "pay attention" to this stimulus. However, there are two alternative interpretations for the lack of an enhanced defensive response in the presence of the distractor: 1) The animals may be conditioned to the context, and the addition of the vibration stimulus represents a different context, which animals distinguish from the training context. 2) The CS + distractor may represent a distinct compound stimulus that was not associated with the tail shock. We reasoned that if the distractor stimulus indeed competed for the animals' attention, causing them to ignore the CS, then the efficacy of the distractor should depend on its novelty. To determine the importance of novelty for an effective distractor, we tested the effect of 5 pre-exposures to the distractor stimulus on the day of testing. Pre-exposure to the distractor largely eliminated its efficacy in reducing the enhanced defensive response to the CS ($p = 0.007$), suggesting that the novel stimulus is indeed "distracting the animals' attention." These results further suggest that in *Aplysia*, much as in humans, including infants, the ability of a stimulus to attract attention strongly depends on the novelty of the stimulus.

Disclosures: K. Pearce: None. **M.E. Kimbrough:** None. **X. Zhao:** None. **T.S. Dehghani:** None. **E.J. Moc:** None. **D. Enayati:** None. **S.S. Bentley:** None. **V. Kong:** None. **T.W. Abrams:** None.

Poster

629. Invertebrate Learning and Memory I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 629.21/BB32

Topic: F.02. Animal Cognition and Behavior

Support: NIH grant SC3GM111188

TAMU-CC college-level research enhancement funds

Title: Prolonged food deprivation alters the co-expression of sensitization and food suppression induced by aversive stimuli in *Aplysia*

Authors: K. A. MAC LEOD, M. L. WAINWRIGHT, *R. MOZZACHIODI;
Dept. of Life Sci., Texas A&M Univ. - Corpus Christi, Corpus Christi, TX

Abstract: Organisms learn to adapt their behaviors in response to environmental stimuli in order to maintain a balance of their energetic needs. Following exposure to aversive stimuli, an organism budgets its behaviors by augmenting defensive responses and reducing/suppressing non-defensive behaviors. For example, in the marine mollusk *Aplysia*, exposure to noxious stimuli concurrently enhances defensive withdrawal reflexes (i.e., sensitization) and suppresses feeding. Recent work has revealed a strong relation in the temporal dynamics of sensitization and feeding suppression, which suggests a mechanistic link between these two processes. In this study, we attempted to uncouple the co-expression of sensitization and feeding suppression by manipulating of the animal's motivational state through prolonged food deprivation. A training protocol, consisting of a single 10-s train of electric shocks to the body wall, induces concomitant sensitization of the tail-siphon withdrawal reflex (TSWR) and feeding suppression in animals food deprived for 2 days. Both behavioral changes last at least 2 h, but less than 24 h. Here, we analyzed whether extending the period of food deprivation to 14 days could alter this co-expression of sensitization and feeding suppression. Four groups of animals were included: trained/14-day food deprived (T-14), untrained/14-day food deprived (UT-14), trained/2-day food deprived (T-2) and untrained/2-day food deprived (UT-2). For each group, TSWR duration and bites in response to a food stimulus were measured prior to and 15 min and 2 h after training. Sensitization of the TSWR was not expressed either 15 min or 2 h after training in T-14 animals, whereas it was observed in T-2 animals at both time points. Notably, prolonged food deprivation did not affect baseline TSWR duration, current threshold to elicit a detectable TSWR, or sensitivity to sensitizing shocks, indicating that the lack of sensitization in T-14 animals was not due to a reduced responsiveness to external stimuli. In contrast to sensitization, feeding suppression was not affected by prolonged food deprivation as it was observed at 15 min and 2 h in both T-14 and T-2 animals. Overall, the above results indicate that prolonged food deprivation

uncouples the co-expression of sensitization and feeding suppression. The lack of sensitization might be ascribed to prolonged food deprivation interfering with biochemical pathways underlying this behavioral change. The persistence of feeding suppression in T-14 animals might represent a strategy in which reducing bites following aversive stimuli could conserve energy in the short term.

Disclosures: **K.A. Mac Leod:** None. **M.L. Wainwright:** None. **R. Mozzachiodi:** None.

Poster

630. Invertebrate Learning and Memory II

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 630.01/BB33

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant 5RO1AG034446

Princeton University's Innovation Award

Title: Identifying neuronal dynamics of short-term associative memory in *C. elegans*

Authors: ***A. SYLVAIN**[1], M. RAHIMI[2], G. STEIN[3], C. T. MURPHY[2];
[1]Princeton Neurosci. Inst., [2]Lewis Sigler Inst. for Integrative Genomics, [3]Mol. Biol., Princeton Univ., Princeton, NJ

Abstract: All animals make decisions based on the information they learn and remember about their environment, which requires neural plasticity. *C. elegans* is able to remember an association between food and odor (butanone) for a short time (less than 2 hours), an ability that is equivalent to classical short-term associative memory (STAM). We have defined many of the molecular components of this process through genetic analyses, but the circuit dynamics of STAM are not yet known. We have found that AWC^{on} exhibits increased odor-evoked Ca^{2+} responses upon STAM training, and that the number of animals responsive to the odorant decreases with increased post-conditioning time in close parallel to that observed in population STAM assays. We developed a novel microfluidic chip to simultaneously assay AWC^{on} activity and animal behavior to test whether the enhanced neuronal response correlates with the behavioral changes, and have identified neurons required for STAM performance. Finally, we have used these tools to begin to address the mechanism underlying *daf-2*'s three-fold increased STAM duration. These studies provide the framework for comprehensively understanding molecular and neural circuit mechanisms of short-term associative memory.

Disclosures: **A. Sylvain:** None. **M. Rahimi:** None. **G. Stein:** None. **C.T. Murphy:** None.

Poster

630. Invertebrate Learning and Memory II

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 630.02/BB34

Topic: F.02. Animal Cognition and Behavior

Title: UNC-43T, a putative ortholog of CaMKII$_\gamma$, appears necessary for associative conditioning in *C. elegans*

Authors: *J. K. ROSE, L. K. ALFILER, M. R. PRIBIC;
Psychology, Western Washington Univ., Bellingham, WA

Abstract: Calcium/calmodulin-kinase II (CaMKII) plays a role in the neuronal plasticity mechanisms that underlie learning. Recently, it has been demonstrated that CaMKII$_\gamma$ functions as a nuclear transporter involved in initiation of gene transcription (Ma et al., 2014). In *C. elegans*, the *unc-43* gene is considered an ortholog of CaMKII. The *unc-43*(gk452) mutant strain carries a specific deletion for the UNC-43T isoform, a putative ortholog of human CaMKII$_\gamma$. Our current results indicate that *unc-43*(gk452) worms show deficits in associative chemotaxis and chemoavoidance, *C. elegans* associative conditioning assays where acquisition of stimulus pairing occurs over the course of 1+ hours. More recently, we have determined that the *unc-43*(gk452) strain also shows impairment for rapidly acquired learning using a newly developed Classical Conditioning protocol that involves delayed presentation of a light stimulus (either UV or blue wavelength light; US) following onset of a vibrational stimulus (100 Hz tone; CS). With this Classical Conditioning procedure, wild-type *C. elegans* show an increased reversal magnitude (CR) to tone alone (CS) when presented one minute after pairing ($p<0.05$). Interestingly, *unc-43*(gk452) worms show a different response pattern after pairing: smaller mean reversal magnitudes as well as decreased response probability ($p<0.05$, $p<0.05$, respectively). These results suggest that CaMKII$_\gamma$ may be a necessary component for associative conditioning in *C. elegans*. Current work includes identifying necessary coding regions as well as determining retention duration.

Disclosures: **J.K. Rose:** None. **L.K. Alfiler:** None. **M.R. Pribic:** None.

Poster

630. Invertebrate Learning and Memory II

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 630.03/BB35

Topic: F.02. Animal Cognition and Behavior

Support: NSERC

Title: lrn-2/scd-2 mutations dissociate sensory integration and associative learning in *C. elegans*

Authors: *G. S. WOLFE[1], V. TONG[2], D. VAN DER KOOY[2];
[1]Inst. of Med. Sci., [2]Mol. Genet., Univ. of Toronto, Toronto, ON, Canada

Abstract: The cellular and molecular mechanisms of learning and memory can be studied in detail by taking advantage of model organisms such as the nematode, Caenorhabditis elegans. With a fully mapped connectome and genetic tractability, *C. elegans* has a wide variety of behaviours controlled by comparatively few neurons. We have characterized an EMS derived mutant strain, lrn-2, which shows deficits in both sensory integration and a wide variety of associative learning paradigms. Mapping, sequencing, complementation tests and wild type gene rescue have localized this mutation to the gene scd-2. Our experiments suggest that while sensory integration and associative learning mechanisms share genes in common, these genes act within independent pathways underlying separable psychological processes. The primary test of associative learning used in this project involved learning about pathogenic bacteria. The N2 control strain learns to associate the pathogenicity of PA14, a strain of P. aeruginosa, with the odor of the bacteria after 4 hour exposure. This results in N2 worms leaving the PA14, and migrating to a safe E. coli lawn on the other side of the plate. The lrn-2 mutants do not learn this association and remain on the pathogenic bacteria. The sensory integration deficit in these same mutant worms is demonstrated by the mutant's inability to integrate two cues by crossing an aversive copper barrier to reach an attractive diacetyl odorant. Both learning and sensory integration involve the processing of multiple sensory cues leading to altered behavioral output. While sensory integration does not require these changes to persist, associative learning requires these changes to persist as memories. lrn-2/scd-2 plays a role in both sensory integration and associative learning; however, we have found that each of these psychological processes require lrn-2/scd-2 expression independently. The gene fsn-1 has been shown to have an upstream suppressive effect on scd-2 sensory integration, but we have found that in an associative learning assay, fsn-1 may act differently, downstream of scd-2. Expression of wild type scd-2 in AIA neurons rescues sensory integration, but not associative learning, indicating that the two processes use different neuronal pathways. These data suggest a dissociation of the mechanisms of sensory integration and associative learning, despite some shared genetic components.

Disclosures: G.S. Wolfe: None. **V. Tong:** None. **D. van der Kooy:** None.

Poster

630. Invertebrate Learning and Memory II

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 630.04/BB36

Topic: F.02. Animal Cognition and Behavior

Support: CSU Fresno FSSRA Grant

Title: Flexibility of the learned antenna projection response to natural contexts in Periplaneta americana

Authors: *M. POMAVILLE[1], D. D. LENT[2], A. LAWLESS[2];
[2]Biol., [1]California State University, Fresno, Fresno, CA

Abstract: The American cockroach, Periplaneta americana, has demonstrable advantages when exploring neural underpinnings of sensory processing, learning and memory. It is often more efficient to experiment on animals such as cockroach, to gain a basic understanding of how form follows function in neural systems. These experiments examine the interaction of multi-modal sensory acquisition, motor control, learning and memory systems and how they are organized in the brain of the cockroach. The antennal projection response (APR) is an established paradigm to explore learning and memory in the cockroach. It has been used to explore the neural basis of associations between olfactory and visual space and how this spatial encoding is integrated with motor cues. An interesting question that has not been addressed is whether measuring APRs or correlating the APR with motor output can be done with freely moving cockroaches, which antennate vigorously most of the time. Natural behaviors in cockroaches likely require learning associations across multiple modalities in an environment enriched with visual, olfactory, and auditory spatial cues. The inclusion of freely moving behaviors, as a complementary approach, to previous studies of associative and spatial learning and memory in the cockroach are providing much needed insight into the flexibility of the APR to a natural context. Here we examine how the learned APR of semi-restricted cockroaches translates to free running choices made during foraging. A series of experiments were performed which examined the visual associative and spatial learning abilities of the cockroach. We examined the effects of full antennal function and with restricted antennal function as well as intact brain animals and animals which had a procedure done to divide the halves of the brain by lesioning the central complex. Both the antennal function and the brain lesions have been shown to have an effect on the type of information learned and the length of resulting memory. Cockroaches were first trained in a semi-restricted setup where they learn to associate visual cues and odor cues. Following training cockroaches were tested in a free moving choice paradigm. Our data suggests that the APR

analyzed in the laboratory context is highly predictive of choices made in the freely moving cockroaches. This data also revealed multiple elements underlying complex spatial learning behavior and choice in foraging, including, the role of unilateral and bilateral sensory acquisition and learning, memory localization within the brain hemispheres, memory transfer and interference, and the interaction of neural systems.

Disclosures: **M. Pomaville:** None. **D.D. Lent:** None. **A. Lawless:** None.

Poster

630. Invertebrate Learning and Memory II

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 630.05/BB37

Topic: F.02. Animal Cognition and Behavior

Support: Grant-in-Aid for JSPS Fellows 15J01414

Grants-in-Aid for Scientific Research 24370030

Title: Crucial evidence of the prediction error theory in a behavioral pharmacological study

Authors: ***K. TERAO**[1,3], Y. MATSUMOTO[4], M. MIZUNAMI[2];
[1]Grad. school of life science, Hokkaido Univ., Sapporo,, Japan; [2]Fac. of Sci., Hokkaido Univ., Sapporo, Japan; [3]Japan Society for the Promotion of Sci., Tokyo, Japan; [4]Fac. of Liberal Arts, Tokyo Med. and Dent. Univ., Ichikawa, Japan

Abstract: In associative learning in mammals, it is widely accepted that the discrepancy, or error, between actual and predicted unconditioned stimulus (US) determines whether learning occurs when a stimulus is paired with a US. Complete evidence for the prediction error theory, however, has not been obtained in any learning systems: Blocking can also be accounted for by other theories. In this study, we obtained unequivocal evidence of blocking and evidence to reject the alternative theories in classical conditioning in crickets. Prediction error theory stems from the finding of blocking by Kamin, who found that when a stimulus (X) is paired with a US in a compound with another stimulus (Y), learning of X is blocked if Y has been previously paired with the US. Kamin argued that the blocking is due to the requirement of surprise for learning, i.e., no learning occurs when the US is fully predicted. This idea was formulated into the prediction error theory. Recent research in mammals has demonstrated that activities of dopamine (DA) neurons in the midbrain mediate reward prediction error signals in classical conditioning and instrumental conditioning. Unambiguous demonstration of the prediction error

theory, however, has not been achieved in any learning systems. Blocking can also be accounted for by other theories, such as attentional theory. Here, we performed behavioral analysis of blocking and obtained evidence to reject attentional theory in crickets. Crickets are newly emerging experimental animals for learning. We previously observed that octopamine (OA) receptor antagonists impair appetitive learning but not aversive learning, whereas DA receptor antagonists impair aversive learning but not appetitive learning. To obtain further evidence supporting the prediction error theory and rejecting alternative theories, we constructed a neural model to match the prediction error theory, and tested a prediction from the model: We noticed that our model predicts that blockade of synaptic transmission from OA neurons by an OA receptor antagonist during a pairing of a stimulus (Y) with reward (Y+ training) impairs learning of Y but not formation of reward prediction by Y. Thus, subsequent Y+ training, after recovery from the synaptic blockade should produce no learning. We observed such an "auto-blocking" in appetitive learning, which could be accounted for by the prediction error theory but not by alternative theories. We also observed an auto-blocking in aversive learning in use of a DA receptor antagonist. This study demonstrates validity of the prediction error theory and providing solid basis to elucidate computational mechanisms of the prediction error.

Disclosures: K. Terao: None. **Y. Matsumoto:** None. **M. Mizunami:** None.

Poster

630. Invertebrate Learning and Memory II

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 630.06/BB38

Topic: F.02. Animal Cognition and Behavior

Title: Are the neural circuits controlling the temporal structure of spontaneous actions involved in operant self-learning?

Authors: C. ROHRSEN, *B. BREMBS;
Univ. Regensburg, Regensburg, Germany

Abstract: Variability is an adaptive and ubiquitous feature of all our behaviors, which is actively regulated according to task demands. Behavioral variability explains why under identical circumstances, individuals are able to initiate different actions. The amount of behavioral variability predicts operant learning performance (e.g., 1-3), because behavioral variability is a necessary prerequisite for operant learning. Tethered *Drosophila* fruit flies exhibit random-like turning attempts in stationary flight (4), which can be operantly conditioned (5). In a first screen, we have identified neurons in the ellipsoid body of the fly brain to be involved in the temporal

structure of these spontaneous turning attempts. We have started a behavioral characterization of flies where these neurons have been genetically manipulated. In particular, we will present results of flies with compromised physiology in these ellipsoid-body neurons in operant self-learning and world-learning experiments. The behavioral experiments are complemented by anatomical characterization of the neurogenetically identified circuits using immunohistochemistry and confocal microscopy. Skinner, B. 1981. Selection by consequences. Science 213:501-504 Grunow, A., and A. Neuringer. 2002. Learning to vary and varying to learn. Psychonomic Bulletin & Review 9:250-258 Wu, H. G., Y. R. Miyamoto, L. N. G. Castro, B. P. Ölveczky, and M. A. Smith. 2014. Temporal structure of motor variability is dynamically regulated and predicts motor learning ability. Nature Neuroscience 17:312-321 Maye, A.; Hsieh, C.; Sugihara, G. and Brembs, B. (2007): Order in spontaneous behavior. PLoS ONE 2(5): e443 Brembs, B. and Plendl, W. (2008): Double dissociation of protein-kinase C and adenylyl cyclase manipulations on operant and classical learning in *Drosophila*. Curr. Biol. 18(15):1168-1171.

Disclosures: C. Rohrsen: None. **B. Brembs:** None.

Poster

630. Invertebrate Learning and Memory II

Location: Hall A

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Program#/Poster#: 630.07/BB39

Topic: F.02. Animal Cognition and Behavior

Support: NINDS Grant 2R37NS19904

NINDS Grant 2R01NS05235

Title: Forgetting is mediated by a dopamine→Scribble→Rac signaling pathway

Authors: *I. CERVANTES-SANDOVAL, M. CHAKRABORTY, R. L. DAVIS;
Neurosci., The Scripps Res. Inst., Jupiter, FL

Abstract: Forgetting of continuously acquired memories is crucial for proper function of the memory system. Nevertheless, little is known about the molecular, cellular and circuit basis for forgetting memories. Here we show that Scribble, a scaffolding protein known primarily for its role as a cell polarity determinant, is required for proper forgetting of olfactory memories in *Drosophila*. Knocking down scribble in either dopaminergic or mushroom body Kenyon cells, important elements of the circuitry for learning and forgetting, impairs normal memory loss. In addition, we show that Scribble functions within Kenyon cells to regulate active forgetting in a

signaling pathway that is activated by extracellular dopaminergic inputs and upstream of the small GTPase Rac. These results place Scribble as a central scaffolding molecule in the emerging signaling system underlying active forgetting.

Disclosures: I. Cervantes-Sandoval: None. **M. Chakraborty:** None. **R.L. Davis:** None.

Poster

630. Invertebrate Learning and Memory II

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 630.08/BB40

Topic: F.02. Animal Cognition and Behavior

Support: Health Research Council of New Zealand

Title: Investigating the histone deacetylase 4 (hdac4) memory pathway: interaction with ankyrin2?

Authors: *S. SCHWARTZ, H. L. FITZSIMONS;
Massey Univ., Palmerston North, New Zealand

Abstract: A growing body of evidence shows that learning and memory are regulated by epigenetic mechanisms. We have previously shown that HDAC4 plays a critical role in memory formation in *Drosophila*, and it is similarly required for memory in mammals, however its specific functions have not yet been elucidated. In an effort to identify genes that interact in the HDAC4 memory pathway, we performed a genetic screen in *Drosophila*. Overexpression of HDAC4 in *Drosophila* photoreceptors results in a mild “rough eye” phenotype, with disorganised ommatidia and bristles. This phenotype is ideal for screening for modifiers of HDAC4 activity, as it is an *in vivo* phenotype that is easily scored and does not affect viability. A panel of 115 candidate RNAi lines were screened and 26 were found to significantly enhance the HDAC4-induced rough eye phenotype. As each individual gene did not itself induce a significant rough eye phenotype, the enhancement of the HDAC4 phenotype would suggest that the gene interacts in the same molecular pathway as HDAC4. The screen confirmed several genes known to interact with HDAC4 in other organisms or tissues, e.g. mef2, creb and 14-3-3ζ, establishing its reliability. Novel HDAC4 interactors were identified including ankyrin2 which was chosen for further investigation as it has been implicated in synaptic stability and in human intellectual disability. In addition, HDAC4 harbours a conserved ankyrin binding domain, suggesting a potential physical interaction. Immunohistochemistry analyses showed that ankyrin2 is strongly expressed in the adult brain where it co-localises with cytoskeletal components futsch and

neuroglian. Like HDAC4, ankyrin2 localises to axons of the mushroom body (MB), a key structure for memory formation in flies. Knockdown of ankyrin2 in the developing brain results in defects in mushroom body development including axon outgrowth and guidance. Further investigation will help elucidate whether an interaction between ankyrin2 and HDAC4 leads to changes in long-term memory formation in flies. In this study we have identified candidate proteins that interact with HDAC4 in neurons. This is fundamental in order to clarify the genetic pathways underlying memory processes and for the contribution to the study of cognitive disorders that disrupt memory, bringing new insights that can lead to new pharmacological treatments.

Disclosures: **S. Schwartz:** None. **H.L. Fitzsimons:** None.

Poster

630. Invertebrate Learning and Memory II

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Topic: F.02. Animal Cognition and Behavior

Support: National Basic Research Project (973 program) of the Ministry of Science and Technology of China 2013CB835100

National Science Foundation of China 91332207

Tsinghua-Peking Joint Center for Life Sciences

Title: Electric-Shock Sensory in *Drosophila* central brain

Authors: *W. HU, Y. PENG, F. ZHANG, L. WANG, Y. ZHONG;
Sch. of Life Sci., Tsinghua Univ., Beijing, China

Abstract: Canonical aversive learning in *Drosophila* uses electric-shock as unconditioned stimulus (US) mostly. It is found that a small group of dopamine neurons mediated electric shock input and converged with the odor signal in mushroom body, but these dopamine neurons do not affect flies sensing and avoiding shock. However, it is not clear about the electric-shock sensing in fly brain. Here we report that a subgroup of central complex neurons highly respond to electric-shock delivered to feet but not abdomen of flies. Acutely blocking these neurons leaded flies to decreased sensitivity of shock in flies, while acutely activating the same neurons could substitute US in aversive training. Our results demonstrate these neurons could be an elementary sensory center for electric-shock.

Disclosures: **W. Hu:** None. **Y. Peng:** None. **F. Zhang:** None. **L. Wang:** None. **Y. Zhong:** None.

Poster

630. Invertebrate Learning and Memory II

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 630.10/BB42

Topic: F.02. Animal Cognition and Behavior

Support: NSERC Discovery #122216-2013

Title: A glycine receptor subunit homologue, AVR-14, alters short-term memory in an interstimulus interval-dependant manner

Authors: ***C. H. RANKIN**, T. MCDIARMID;
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Abstract: Habituation is a learned decrement in responding following repeated exposure to a stimulus. Despite its importance the mechanisms underlying habituation remain largely unknown. Repeated exposure to taps (non-localized mechanosensory stimulation) leads to habituation of a reversal withdrawal response in *C. elegans* that is dependent on glutamate transmission. Here we use high throughput behavioural analysis to characterize the role of AVR-14, an inhibitory glutamate gated chloride channel homologous to vertebrate glycine subunits that is expressed on the mechosensory neurons. avr-14 loss of function mutants display a larger initial reversal duration in response to tap and faster habituation to tap stimuli than wild-type animals at a 10s interstimulus interval (ISI). At long ISIs (60s), avr-14 mutants habituated significantly less than wild-type animals. The stark contrast in phenotypes at short and long ISIs necessitated analysis of habituation across ISIs (10-60s ISIs). This revealed that mutations in avr-14 result in faster habituation at short ISIs, wild-type habituation at intermediate ISIs, and slower habituation and longer ISIs. Together these studies suggest mutations in avr-14 alter habituation in an ISI-dependent manner. Experiments using cell-specific knockdown, rescue, and stimulation will localize the memory functions of AVR-14 to elucidate how it modulates the tap habituation circuit. These studies will determine how the inhibitory functions of glutamate mediate short-term habituation in *C. elegans*, furthering our understanding of the processes underlying learning and memory.

Disclosures: **C.H. Rankin:** None. **T. McDiarmid:** None.

Poster

630. Invertebrate Learning and Memory II

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Topic: F.02. Animal Cognition and Behavior

Support: JSPS KAKENHI Grant Number 15K18577

Grant for Basic Science Research Projects from The Sumitomo Foundation

Title: Dopamine receptor activities regulate learning-dependent odor preference changes in *Drosophila*

Authors: *S. NAGANOS, M. SAITOE;
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Abstract: Experience-dependent preference changes often happen to animals through either a good or a bad experience. Such phenomena also occur even in *Drosophila*. Olfactory conditioning is an example of such experience-dependent preference changes, and we use two aversive conditioning odors (CS) to condition flies; flies are sequentially exposed to the first CS+ odor with electrical shocks and the second CS- odor without electrical shocks. In this study, we found two classes of memory components, memory for avoiding CS+ (CS+ memory) and memory for approaching CS- (CS- memory), after single cycle olfactory conditioning. Importantly, without CS+ memory formation, flies still avoid CS- odor, suggesting that significance of CS- odor for flies is changed by previous experience. In addition whereas CS+ memory was maintained more than 3hr, CS- memory was declined within 3hr. We explored molecular mechanisms concerned with these memory formations by employing well-established olfactory memory mutants. As a result, we found that mutations in D1 type dopamine receptor (D1R) gene disrupt both CS+ and CS- memory formation. Therefore, to explore the brain regions required for CS+ and CS- memory formation, we employed GAL4/UAS binary system, which allows us to manipulate D1R expression in specific brain regions. We found that D1R function in the mushroom bodies (MBs), neural center for olfactory memory formation, is necessary for CS+ memory but not for CS- memory. Especially, D1R activity in γ lobes but not in α / β and α' / β' lobes is sufficient for CS+ memory formation. In contrast, D1R function in the projection neurons (PNs) in the antennal lobes (ALs), the primary olfactory center, is required for CS- memory but not for CS+ memory. These results suggest that although both CS+ and CS- memory require D1R activity they are formed in different brain regions.

Disclosures: S. Naganos: None. **M. Saitoe:** None.

Poster

630. Invertebrate Learning and Memory II

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Program#/Poster#: 630.12/BB44

Topic: F.02. Animal Cognition and Behavior

Support: USDA/NIFA grant 010-65105-20625

NIMHD grant 2G12MD007592

RISE grant R25 GM 069621

Title: Octopamine in Sexual Behavior

Authors: *A. I. FERNANDEZ[1], J. LIM[1], J. JAMES[1], P. EVANS[2], K.-A. HAN[1];
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Abstract: Octopamine (OA) is a monoamine that acts as a neuromodulator in invertebrates and is homologous to norepinephrine in mammals. OA modulates numerous physiological processes such as motivation, pheromone response, olfaction, learning and memory in the fruit fly *Drosophila* melanogaster. The aim of our study is to understand the mechanism by which OA regulates various aspects of sexual behavior. *Drosophila* has four known OA receptors OAMB, Octβ1R, Octβ2R, and Octβ3R. To achieve the goal we investigated basal and high order courtship behaviors of the flies deficient in individual OA receptors or OA biosynthesis. Basal courtship analysis was performed by examining a male's behavior towards a female and measuring the latency and duration of courtship and copulation. To study the role that OA has on the learning and memory processes, a conditioned courtship test was performed. The test measures the ability of the male to learn and remember aversive courtship experience. When subjected to the assays, the OA receptor mutants oamb, octb1r and octb2r exhibited delayed courtship and copulation latency, reduced courtship index and altered copulation duration. On the other hand, oamb but not the other receptor mutants show impaired learning. Studies are in progress to identify the relevant neural sites that the OA receptors regulate the sexual behavior. This study was supported by the USDA/NIFA grant 010-65105-20625, NIMHD grant 2G12MD007592 and the RISE grant R25 GM 069621 grants.

Disclosures: **A.I. Fernandez:** None. **J. Lim:** None. **J. James:** None. **P. Evans:** None. **K. Han:** None.

Poster

630. Invertebrate Learning and Memory II

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Program#/Poster#: 630.13/BB45

Topic: F.02. Animal Cognition and Behavior

Support: NIMHD Grant 2G12MD007592

Title: The roles of dopamine in sexual behavior

Authors: *J. LIM, J. JAMES, J. JOHNSON, K.-A. HAN;
Univ. of Texas At El Paso, El Paso, TX

Abstract: Dopamine (DA) is an important monoamine neuromodulator in the central nervous system of both invertebrates and mammals. It regulates motivation, reward, disinhibition, learning and memory and sexual behavior. However, the neural sites where individual dopamine receptors function to modulate these behaviors need to be clarified. The goal of our study is to understand the neural and cellular mechanisms that dopamine regulates sexual behavior. To address this, we have used the genetically tractable model organism *Drosophila* melanogaster and examined basal and high order courtship behaviors of the flies deficient in individual DA receptors or DA transporter (DAT). They include the D1 receptor mutants dumb1 and dumb2, D2 receptor mutant dd2r, dopamine/steroid ecdysone receptor mutant der, D5 receptor mutant damb, and DAT mutant fmn. Wild type naïve male flies usually respond to distinct incoming sensory inputs and actively court virgin females. D1 receptor mutants, however, show altered courtship activity. Studies are in progress to identify the neural sites that the D1 receptors play a role in sexual behavior. This work was supported by the National Institute of Minority Health and Health Disparity grant 2G12MD007592.

Disclosures: J. Lim: None. **J. James:** None. **J. Johnson:** None. **K. Han:** None.

Poster

630. Invertebrate Learning and Memory II

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Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant GM067310

Title: Hormonal convergence in regulation of *Drosophila* courtship memory

Authors: *S.-S. LEE[1], N. KARAPETIANS[1], C. RIVERA-PEREZ[3], T. WIJESEKERA[4], F. G. NORIEGA[3], B. DAUWALDER[4], M. E. ADAMS[2];
[1]Neurosci., [2]Cell Biol. & Neurosci. and Entomology, Univ. of California, Riverside, Riverside, CA; [3]Biol. Sci., Florida Intl. Univ., Miami, FL; [4]Biol. and Biochem., Univ. of Houston, Houston, TX

Abstract: Formation and expression of memories are critical for context-dependent decision-making. In *Drosophila*, courting males that experience repeated rejection by mated females court less avidly when paired subsequently with virgin females. Both short-term and long-term memories associated with rejection have been demonstrated; here we show that hormonal state is critical for both. Ecdysis triggering hormone (ETH) appears to be essential for male courtship memories via two signaling pathways: one is indirect through promotion of juvenile hormone (JH) synthesis, while the other is direct through action on mushroom body neurons. With regard to the indirect pathway, suppression of JH levels by ETH receptor (ETHR) silencing in corpora allata of males leads to both short-term and long-term courtship memory deficiencies, both of which are rescued following treatment of JH analog methoprene. Our evidence shows that JH is essential for 1) sensing aversive male-specific chemical cues from mated females and 2) recognition of behavioral cues provided by the mated female. Conditional gene expression and age-dependent rescue experiments demonstrate a critical period for JH action in memory formation. JH-dependent long-term courtship memory requires expression of JH receptors Met and Gce in mushroom body neurons. Evidence for a direct role of ETH signaling in long-term memory formation comes from its suppression by silencing ETHR in mushroom body neurons. Block of ETH release from Inka cells also negatively affects memory performance, confirming that hormonal signaling is required for memory formation. Our findings indicate that ETH promotes convergent signaling pathways contributing to "state-dependent" learning and memory of social context.

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Poster

630. Invertebrate Learning and Memory II

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Support: USDA/NIFA grant 010-65105-20625

NIH-NIGMS grant 2T34GM008048

Title: The role of beta adrenergic-like octopamine receptor Octβ1R in learning and memory

Authors: *J. B. SABANDAL[1], P. EVANS[2], K.-A. HAN[1];
[1]The Univ. of Texas At El Paso, El Paso, TX; [2]The Inositode Lab., The Babraham Inst., Cambridge, United Kingdom

Abstract: Octopamine, the invertebrate counterpart of mammalian norepinephrine, is a major monoamine in invertebrates and plays a critical role in learning and memory. Previous studies show that octopamine is crucial for appetitive memory formation, but its role in aversive learning and memory is not fully characterized. In order to identify octopamine's role in aversive learning and memory in *Drosophila* melanogaster, we employed negatively reinforced olfactory classical conditioning in which flies were presented with an odor (conditioned stimulus +) paired with an aversive stimulus, electric shock (unconditioned stimulus). They were then presented with another odor without shock. To test the capacity of the flies to learn and remember, flies were transferred into the apparatus called T-maze and presented with the two odors on opposite sides of the apparatus. This decision-making process measures whether flies were able to distinguish the odor paired with shock and avoid it. Performance indices were calculated by subtracting the number of flies that made the incorrect choice (odor with shock) from the correct choice (odor without shock), divided by the total number of flies. Wild-type Canton-S flies performed well in learning and short-term memory tests. However, the flies lacking the octopamine receptor Octβ1R exhibited poor learning but normal memory decay. This suggests that Octβ1R is essential for aversive olfactory learning but not for short-term memory. The studies are in progress to identify the critical neural site where Octβ1R regulates aversive learning.

Disclosures: J.B. Sabandal: None. **P. Evans:** None. **K. Han:** None.

Poster

630. Invertebrate Learning and Memory II

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Program#/Poster#: 630.16/BB48

Topic: F.02. Animal Cognition and Behavior

Title: Serotonergic modulation of goal-directed habituation during exploration in *Drosophila*

Authors: *G. W. ROMAN[1], S. ZHANG[1], M. DE LA FLOR[1], L. CHEN[1], G. GUNARATNE[1], H. DIERICK[2];
[1]Univ. Houston, Houston, TX; [2]Baylor Col. of Med., Houston, TX

Abstract: Novel environments elicit exploratory behaviors in many species. These behaviors allow the animal to gather information about its environment, and are likely to have a strong adaptive value. As the animal explores, goal-directed habituation of the novelty stimulus leads to a gradual decrease in exploratory behaviors. We use the open field arena behavior of *Drosophila* to understand how goal-directed habituation can be modulated to alter the amount of exploration. When *Drosophila* are placed within a novel open field arena, the fly explores the arena's boundary. During exploration, *Drosophila* display high levels of activity and a directional persistence. As the fly visits each segment of the arena boundary, the novelty is habituated and both directional persistence and mean absolute activity decay to spontaneous activity levels. Serotonin is a bidirectional modulator of the rate of goal-directed habituation during exploration. Increasing the activity of serotonergic neurons through the targeted expression and activation of the TrpA1 channel or the ectopic expression of the NaChBac sodium channel resulted in a significant increase in novelty habituation. Moreover, increasing serotonin levels by feeding flies the serotonin precursor 5-HTP also significantly increased the rate of habituation. These effects of increasing serotonin are reverted 72 hours after feeding the flies' 5-HTP, indicating a temporary effect on habituation. Interestingly, decreasing the activity of the serotonergic neurons by hypo-polarizing with the targeted expression of the Kir2.1 channel resulted in decrease in habituation and a consequent increase in the amount of exploration. Pharmacologically reducing serotonin levels by feeding the inhibitor of serotonin biosynthesis alpha-methyl tryptophan also decreased the rate of habituation in the open field arena. Mutations in the 5HT1A and 5HT1B receptors also display reduced levels of habituation and increases in exploration, and these mutations effectively block the effect of 5-HTP feeding on the rate of habituation. The overexpression of 5HT1A and 5HT1B in subsets of the central nervous system also drives increased rates of habituation. Together, these results suggest an important role for serotonin in modulating the rate of goal-directed habituation during the exploration of novel environments.

Disclosures: G.W. Roman: None. **S. Zhang:** None. **M. de la Flor:** None. **L. Chen:** None. **G. Gunaratne:** None. **H. Dierick:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: F.02. Animal Cognition and Behavior

Support: Brain & Behavior Research Foundation (D.F.)

NIMH (D.F.)

National Science Foundation (D.S.)

Title: Mechanisms contributing to experience-dependent changes in the structure of hippocampal replay sequences

Authors: *T. FENG, D. SILVA, D. FOSTER;
Neurosci., Johns Hopkins Univ. SOM, Baltimore, MD

Abstract: Hippocampal replay is a phenomenon that occurs mainly during sharp-wave ripple events, in both awake and sleep states, in which place cells are active in precise sequences. These sequences represent temporally compressed depictions of movement trajectories through navigable space. However, the mechanisms by which such activity patterns are generated with increased experience remain largely unknown. Here we applied high-density electrophysiological recording techniques to examine the development of the fine temporal structure of replay between individual experiences from rats exploring on a novel linear track. As reported previously, significant replays emerged during early experience, that is, immediately after the first running lap on a novel linear track, and covered the whole length of the track. However, the pattern of early replays differed from later replays. Specifically, the speed at which hippocampal replay traversed a linear track slowed down when the animal gained familiarity with a novel environment. By contrast, hippocampal pyramidal cells maintained constant firing rates, while emitting more spikes and being more active during late replays than early replays. The dissociation between place cell firing rate and the speed of replay indicates that certain models of neuronal sequence generation, such as synfire chains, or continuous attractor models with global inhibition, may not be sufficient to represent the underlying mechanism of replay. Moreover, consistent with another on-going study in our laboratory (Pfeiffer BE & Foster DJ), in which the trajectory of replay in a familiar environment was discretized in alternating states of static representation and rapid movement, and phase-locked to the slow-gamma (25-50Hz) rhythm, replays during early exploration of a novel environment were also modulated by slow-gamma oscillations. Further, the number of discrete alternating states in replay increased with experience, accompanied by an increase of the duration of the static representation states and a decrease of the duration of the rapid movement states. In conclusion, hippocampal replay may undergo rapid plasticity with experience, and the change of propagation speed of replay involves fine structural change of the discretized represented trajectory.

Disclosures: **T. Feng:** None. **D. Silva:** None. **D. Foster:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 631.02/BB50

Topic: F.02. Animal Cognition and Behavior

Support: NIMH

Title: Auto-associative dynamics in the generation of sequences of hippocampal place cells

Authors: *B. E. PFEIFFER[1,2], D. J. FOSTER[2];
[1]Neurosci., Univ. of Texas Southwestern Med. Ctr., Dallas, TX; [2]Soloman H. Snyder Dept. of Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Neuronal circuits can produce self-sustaining sequences of activity patterns, but the precise mechanisms remain unknown. It has long been hypothesized that an auto-associative (self-connected) network of recurrently excitable neurons can retrieve discrete memories as attractors (networks whose activity evolves over time to a small number of stable patterns or states). However, sequence retrieval is more problematic to model computationally, since errors in the recovery of each item of information will result in poor recovery of the next item in the sequence; over multiple sequential items, such errors can amass to a catastrophic collapse of the sequence. A theoretical solution is to embed auto-association error-correction for each item within a wider hetero-associative loop for sequence propagation, thereby allowing each item to be accurately represented via attractor network dynamics before transitioning to the next item in the sequence. Information encoded by such a process would be expected to result in "jumpy" sequences that sharpen individual item representations before transitioning to successive items; however, direct evidence for such theoretical processes is lacking, due in large part to the difficulty of obtaining data from very large ensembles of neurons expressing internally-generated sequences recorded at the time resolution of neuronal dynamics. Here we provide the first direct evidence for auto-associative dynamics in sequence generation. During sharp-wave/ripple (SWR) events, hippocampal neurons are known to express sequenced reactivations, and we now show that these reactivations are composed of discrete attractors. Each attractor corresponds to a single location, the representation of which sharpens over the course of several milliseconds, as the reactivation focuses at that location. Subsequently, the reactivation transitions rapidly to a spatially discontiguous, but adjacent new location. This alternation between sharpening and transition occurs repeatedly within individual SWRs, and is locked to the slow-gamma (25-50Hz) rhythm. These findings validate long-standing theoretical notions of neural network function, as well as reveal a fundamental discretization in the retrieval of memory in the

hippocampus, together with a novel function for gamma oscillations in the control of attractor dynamics.

Disclosures: B.E. Pfeiffer: None. **D.J. Foster:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Hall A

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Topic: F.02. Animal Cognition and Behavior

Support: NIMH

Brain Research Foundation

Title: Hippocampal area CA3 is necessary for the induction of sharp-wave ripples in area CA1

Authors: *H. DAVOUDI[1], D. J. FOSTER[2];
[1]Dept. of Biomed. Engin., [2]Dept. of Neurosci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Hippocampal area CA1 local field potential exhibits high frequency (100- 250 Hz) events known as Sharp-Wave Ripples (SWRs). These events that occur during slow-wave sleep and awake restfulness have been shown to be important for the consolidation of spatial memory. However, the mechanism of formation of SWRs is not yet well understood. Although it is hypothesized that projections from the highly recurrent network of the hippocampal area CA3 might be responsible for the formation of SWRs in CA1, this has not been causally demonstrated. In a study by Nakashiba et al. (2009), in which CA3's Schafer Collateral (SC) projections to CA1 were genetically silenced over the time course of a few days, the number of SWRs did not change, while the peak frequency of a fraction of SWRs decreased. However, the time course of genetic silencing in that study was sufficient to allow for the possibility of compensatory mechanisms in the development of ripple activity in CA1. We hypothesized that a more acute shutdown of CA3 input to CA1 might reveal a more significant role. Therefore, we bilaterally expressed proton pump Arch3.0 in SC of 2-3 months old Long-Evans rats. Here we report that, using multi-tetrode recording and reversible optogenetic manipulation, the silencing of SC terminals in CA1 decimates SWRs. In particular, SWRs and their associated spiking activity were abolished when light was delivered to CA3 terminals in CA1 but intact when light was off. Meanwhile, activities in other frequency bands were not affected by light. These

findings shed light on the functional interconnections between hippocampal subregions that support episodic memory.

Disclosures: H. Davoudi: None. **D.J. Foster:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: F.02. Animal Cognition and Behavior

Support: NIMH

Brain Research Foundation

Title: Rate of reverse, but not forward hippocampal replay increases with a relative increase in reward

Authors: *E. AMBROSE[1], B. E. AMBROSE[2], D. J. FOSTER[1];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Replay, the sequential activity of place cells during sharp wave ripples (SWRs) in the hippocampus, may be a mechanism by which current experience is encoded into episodic memory. Replay sequences are capable of reflecting many paths through an environment, of varying length and in the forward or reverse direction, but whether specific types of sequences play different roles in behavior and memory is unknown. Furthermore, the occurrence and content of replays has not been correlated to any particular behavior or context, although it has been shown that sequences can be biased toward a remembered goal location. Using tetrode recording to simultaneously monitor the activity of large ensembles of hippocampal CA1 pyramidal cells in behaving rats, we demonstrate that altering reward contingency in an environment is reflected by changes in SWRs, the overall production of replays, and dynamic shifts in the content of those replays. In agreement with previous studies we find that the rate of SWRs is decreased in the absence of reward and increased to a larger reward, and hippocampal replay also changes in a similar way. However, in the presence of increased reward, the behavior of forward and reverse replays diverges. The rate of reverse replay is relatively increased at that location, while the rate of forward replay is unchanged. Reward strengthens the encoding of salient behavioral episodes, and we suggest that reverse replays may serve to promote encoding

of behaviors which resulted in reward while forward replays may have a different function such as planning.

Disclosures: **E. Ambrose:** None. **B.E. Ambrose:** None. **D.J. Foster:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Hall A

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Program#/Poster#: 631.05/BB53

Topic: F.02. Animal Cognition and Behavior

Title: Seeing the woods for the geometries: The hippocampus is necessary for configural but not elemental cue use in spatial orientation

Authors: *I. N. JOHNSTON;
Sch. of Psychology, The University of Sydney, Australia

Abstract: A custom-built Olton 8-arm radial maze was used to study free-operant spatial behaviour in the rat. On each trial, one arm of the maze was randomly designated the 'active' arm, and the rat received 10-sec access to sucrose from an automated fluid dispenser in a cup at the end of the arm. After the reinforcer had been delivered, the next trial began and another arm was randomly designated as the active arm, and this procedure was repeated for each subsequent trial. In addition to this, white curtains surrounded the maze and an overhead data projector with a wide-angled lens projected an oblique triangular array of black and white cues onto the curtains around the maze. On each trial, these cues were rotated so they remained in a consistent spatial configuration with the active arm. The results of these experiments indicate that: 1. The rats made significantly fewer errors in finding the active arm in the presence of the visuospatial cues compared to trials when they were absent; 2. The number of errors increased in probe trials when elements of the visuospatial configurations were removed. 3. When elements of the configuration were transposed but maintained the shape of the array, the rats preferred the arm indicated by the geometric shape of the array rather than the elements that would normally be closest to the goal. Moreover, temporary inactivation of the hippocampus with muscimol did not affect performance with the single elemental cues, but did impair performance with the configural cues. These studies suggest that rats can use virtual cues to orient themselves towards a goal location, and do so via the geometric properties of an array.

Disclosures: **I.N. Johnston:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Hall A

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Program#/Poster#: 631.06/BB54

Topic: F.02. Animal Cognition and Behavior

Support: NIH AA 019462

Title: Assessing movement similarity in the morris water task

Authors: *D. BARTO, D. HAMILTON;
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Abstract: Performance in the Morris Water Task (MWT) is usually depicted through latency and path length to reach the hidden platform. While these latency and path length measures are useful for molar aspects of performance they fail to capture the qualitative aspects of the rat's trajectory. Examining the changing curvature of path trajectories could reveal movement patterns that emerge as a rat learns to navigate to a hidden platform in the MWT. Identifying these patterns, and to what degree they deviate from an optimal path provides detailed information about an individual rat's movement sequence. The present study plotted the rats' path trajectories and utilized a dynamic time-warping algorithm to assess similarity between path trajectories on successive trials from a single release point. Rats completed 60 trials (12 per day, 4 release points) of hidden platform MWT training. The results indicate that a similar pattern of movement emerges between the 2nd and 3rd training trial for release points located far from the platform. Additionally, path trajectories became significantly dissimilar between training days suggesting a 24-hour forgetting effect. These results illustrate how assessing similarity between path trajectories can capture the idiosyncratic movement patterns that emerge within rats as they learn goal directed navigation.

Disclosures: D. Barto: None. **D. Hamilton:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

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Title: The roles of the medial and lateral divisions of the entorhinal cortex in visual scene memory

Authors: *S.-W. YOO, I. LEE;
Brain and Cognitive Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: The medial and lateral divisions of the entorhinal cortex (the MEC and LEC, respectively) might provide functionally segregated inputs to the hippocampus; that is, the MEC might provide spatial information and the LEC might send nonspatial item information. We have previously shown that the dorsal hippocampus is critical for making scene-dependent decision making. However, it is unclear whether background visual scene information is processed predominantly in the MEC or LEC, or both. We investigated whether the MEC and LEC might play differential roles in processing scene memory in the current study. Specifically, we ran five rats (male Long-Evans) in a scene-based memory task. A T-maze was surrounded by a set of three adjacent LCD monitors and a start box was attached to the stem of the T-maze. Once a trial started, the rat exited the start box and a visual scene was displayed in the LCD monitors. The rat was required to choose one of the food wells in either the left or right arm in association with the displayed visual scene to obtain food reward. Two visual scenes (zebra and pebbles patterns) were used for initial training (40 trials). Once the rats were trained to criterion (>80% correct response per scene and response bias <15%) for two consecutive days, the rat was trained with the second pair of scenes (bamboo and mountain patterns) to criterion. Then, the rat was trained with those four scenes to criterion before surgical implantation of a custom-made 3D cannula complex for targeting both LEC and MEC bilaterally within the same animal. Once the rats (n=5) recovered from surgery (7 days), it was retrained to pre-surgical performance criterion for four scenes. Afterwards, when the rat was injected with either vehicle solution (artificial cerebrospinal fluid, or ACSF) or muscimol (MUS) before testing (0.3uL per site), the MUS injected in either LEC or MEC produced performance deficits ($p<0.01$ and $p<0.05$ for LEC and MEC, respectively), compared to ACSF-injected conditions in the same rat. In three animals, we also tested whether inactivation of the LEC or MEC impaired scene trace memory by turning off the scene stimulus when the rat passed one of the three sensors along the track. In the trace

memory task, it appears that the whole EC (MEC+LEC) inactivations produce the biggest deficits, compared to the vehicle condition, and the MEC inactivations result in bigger trace memory deficits than the LEC inactivations. These results need to be confirmed with more subjects, but our tentative conclusion is that the MEC plays bigger roles in processing visual scene memory than the LEC especially when scene information needs to be kept in working memory for some time for upcoming behavioral choice.

Disclosures: **S. Yoo:** None. **I. Lee:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 631.08/BB56

Topic: F.02. Animal Cognition and Behavior

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Title: The perirhinal cortex, but not the postrhinal cortex, is required for visual, but not tactile, object recognition memory

Authors: *J. AHN, I. LEE;
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Abstract: The rodent perirhinal cortex (PRC) and postrhinal cortex (POR) may provide functionally differential inputs to the hippocampus. PRC, but not POR, might play important roles in object recognition memory. Most prior studies, however, used a spontaneous object exploration paradigm in which animals freely explore old and new objects in an environment. In the current study, we used an explicit object memory task to compare the roles of PER and POR in the same rats. Specifically, rats (n=7) were trained in a task in which a toy object (ice cream or burger) attached to a sand-filled jar must be recognized for correct choice (pushing or digging) to be made to the jar. Only the correct response type associated with the object allowed the rat to

obtain reward. Once the animals were trained to criterion (> 75% correct for each object), they underwent surgery to receive implantation of a custom-made cannula complex targeting both PRC and POR bilaterally. Following recovery from surgery, rats were retrained to criterion, and artificial cerebrospinal fluid (ACSF) was injected in the PRC bilaterally before testing. On the next day, muscimol (MUS) was injected to inactivate the same region. The PRC inactivation yielded deficits initially, but performance improved gradually to control level in the second half of the session. The same injection protocol was repeated for the POR, but the POR inactivation only minimally affected performance. Choice latency (measured from track entrance to response initiation) did not differ between ACSF and MUS conditions. Since the MUS-induced deficit in the PRC mostly appeared in the earlier part of the session, it is possible that the rat switched between different cognitive strategies (e.g., from a visual to tactile strategy) within a session. This possibility was explored by encasing the objects in a transparent acrylic box to bias the rat to use only visual, but not tactile information. PRC inactivation produced sustained impairment through the second half of the session, whereas POR inactivation did not. When rats were tested in complete darkness, however, rats were not affected by MUS in either PRC or POR, suggesting that the performance deficits associated with PRC inactivations were specific to visual modality. The rats were subsequently trained in a simple object discrimination task and the PRC-inactivated rats performed normally, suggesting that MUS in the PRC left visual perceptual memory intact. Taken together, these results implicate that the PRC, but not the POR, is required for conditional behavioral choice based on visual, but not tactile, object memory.

Disclosures: J. Ahn: None. **I. Lee:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: F.02. Animal Cognition and Behavior

Support: Basic Research Grant of Shenzhen city government (JCYJ20140901003938992)

Title: Synchronization between hippocampus and prefrontal cortex during social behavior

Authors: *Y. ZHAN, Y. TANG;
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Abstract: Recent electrophysiological studies in rodents have implicated hippocampal-prefrontal connectivity in anxiety, spatial learning and memory-related tasks. In this study we used *in vivo*

electrophysiological recordings of local field potentials in prefrontal cortex and hippocampus, two structures implicated in the social interaction and exploration, to measure functional connectivity during social interaction behavior. LFP coherence between prefrontal cortex and hippocampus as well as between left and right hippocampus was significantly reduced in *Cx3cr1*$^{-/-}$ mice, a mouse model for microglia-dependent synaptic pruning, across a wide frequency range. Next, we used Granger causality to examine the directionality of information between hippocampus and prefrontal cortex. During social interaction persistent higher PFC driving to dorsal HPC was found. *Cx3cr1*$^{-/-}$ mice showed reduced baseline PFC driving to dorsal HPC. PFC to dorsal HPC causality could predict the actual time spent interacting with the social stimuli. To investigate the consequence of disrupting the synchronization between the hippocampus and the prefrontal cortex, we used optogenetic tools to silence nucleus reuniens, a midline thalamic structure which is thought to mediate the communications between the hippocampus and the prefrontal cortex. When the nucleus reuniens was inhibited, the mice showed reduced time spent with the social stimulus compared to the control animals when they explored a three chambered social interaction box. In the subsequent social novelty test when another novel social stimulus was introduced to the test, inhibiting the nucleus reuniens did not produced deficits in discriminating the two social stimuli. These results point to a role of nucleus reuniens in social behavior, possibly by mediating the information processing between the hippocampus and the prefrontal cortex.

Disclosures: **Y. Zhan:** None. **Y. Tang:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: F.02. Animal Cognition and Behavior

Support: JHU KSAS

Title: Dorsal hippocampus is unnecessary for the expression of either a place or response spatial strategy in the rodent submerged T-maze

Authors: ***J. S. ASEM**, P. C. HOLLAND;
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Abstract: The ability to navigate in one's environment is critical to survival, be it in order to acquire positive reinforcers_ food, water, mates, shelter, sleep_ or to escape negative

consequences_predation and pain. Spatial navigation is commonly examined using the T-maze, in which experimenters are able to dissociate two distinct strategies that are exhibited by animals when acquiring the location of a goal. Previous work has shown that animals exhibit inverse behavioral patterns when appetitively and aversively motivated. In the food-rewarded (dry) T-maze, rats initially adopt a flexible, hippocampal-dependent place strategy, later switching to an automatic, striatal-dependent response strategy (Packard & McGaugh, 1996). However, in an escape-motivated (submerged) T-maze, rats exhibit the opposite pattern: initially adopting a response strategy, and later switching to a place strategy with extended training (Asem & Holland, 2013). Recent work suggests that the role of the dorsolateral striatum in the submerged T-maze is a subtle one: necessary for the early acquisition, but not expression, of the initial response strategy (Asem & Holland, 2015). However, the role of the dorsal hippocampus in the observed behavior has not yet been explicated. The hippocampus has been implicated many times over in spatial learning and navigation as well as rapid, even one-trial, learning. Critically, these results provide conflicting predictions for the submerged T-maze. If the hippocampus is critical for rapid, initial learning, the hippocampus subserves the immediate response strategy. If the hippocampus is critical for spatial and relational information, its recruitment in the submerged T-maze is a gradual one. We sought to investigate whether the role of the dorsal hippocampus is similar in the submerged T-maze as that in the dry T-maze. In Experiment 1, we examined performance of rats receiving either a lidocaine or saline infusion to the dorsal hippocampus immediately prior to probe tests. We observed no effect of drug condition on behavior exhibited during probe tests, suggesting that the dorsal hippocampus is not required for the expression of either behavior. In Experiment 2, we confirmed the effectiveness of the infusion protocol in a positive control task with the same subjects. In Experiment 3, we examined immediate early gene expression in subregions of the hippocampus in subjects expressing a response or place strategy after early or late training.

Disclosures: **J.S. Asem:** None. **P.C. Holland:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: F.02. Animal Cognition and Behavior

Support: Etoiles Montantes Amidex/ANR investissement d'avenir

ERC starting grant

Title: Role of visual cues in idiothetic and allocentric strategies for spatial position coding in hippocampus

Authors: *J. KOENIG, M. NOUGUIER, G. MARTI, F.-X. MICHON, J. EPSZTEIN; INMED/INSERM, U901, Marseille, France

Abstract: Hippocampal place cells can use two strategies to generate their typical space modulated firing patterns: idiothetic and allothetic coding. Idiothetic coding relies on internal cues generated by self-motion (proprioceptive cues, vestibular cues, optic flow) while allothetic coding relies on cues from the external world (visual, tactile and olfactory cues). Both strategies can be used to calculate an animal's location in an environment. We are interested in understanding the environmental attributes that determine the use of one spatial coding strategy over the other by hippocampal place cells and notably the role of proximal visual cues. To address this question we used virtual reality which enables the selective modification of proximal visual cues without altering inputs from other sensory modalities. Head-fixed C57 BL6 mice were trained to run on a polystyrene ball surrounded by screens on which a virtual linear track was displayed. Ball movements were used to update the position of the mice's avatar in the virtual linear track. Mice were trained to go back and forth for liquid rewards in one of four virtual linear tracks (275 cm long) which differed in the availability of proximal, proximo-distal or distal visual cues. Once a stable performance was reached (~ 3 rewards per minute), acute silicon probe recordings were performed to determine the coding strategy used by place cells in area CA1 and CA3 of the hippocampus. The influence of experience on coding strategy was also investigated.

Disclosures: J. Koenig: None. **M. Nouguier:** None. **G. Marti:** None. **F. Michon:** None. **J. Epsztein:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

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Title: Ventral hippocampus inactivation impairs goal-directed spatial navigation in obstacle-laden environments

Authors: M. CONTRERAS[1], T. PELC[1], M. LLOFRIU[2], A. WEITZENFELD[2], *J.-M. FELLOUS[1];
[1]Psychology, Univ. of Arizona, Tucson, AZ; [2]Computer Sci. and Engin., Univ. of South Florida, Tampa, FL

Abstract: Most lesions studies that show a dorso-ventral double dissociation find that ventral but not dorsal hippocampus lesions affect emotional behavior, while dorsal but not ventral hippocampus lesions impair spatial memory and navigation. Electrophysiology studies have also shown that ventral hippocampal cells have lower spatial selectivity and larger place fields than dorsal cells. However, most of the experiments performed to assess the dorsal and ventral contributions to spatial navigation have employed relatively simple tasks that may not have required a strong coordination along the dorso-ventral hippocampal axis. In this study, we tested the hypothesis that the ventral hippocampus may be critical for goal-directed navigation in rich, obstacle laden environments. We trained rats to get rewards from feeders positioned at the periphery of an open-field. After the animals learned a specific set of feeders, we placed small or large obstacles on the maze before the memory recall phase. We report that bilateral ventral hippocampal inactivation (2.5% Bupivacaine or 0.9% saline solution; 1μl per side) impaired spatial navigation in both large and small obstacle conditions. This effect was larger when small objects where present compared to the large objects configurations. Importantly, this impairment did not result from a deficit in the spatial memory for the set of feeders (i.e. recognition of the goal locations) because ventral hippocampus inactivation did not affect recall performance when there were no obstacles on the maze. Furthermore, inactivation of the dorsal hippocampus produced only a minor deficit in large, but not in small obstacle configurations. These results show that, the ventral hippocampus supports spatial navigation when obstacles are present in the environment suggesting that this portion of the structure is necessary to compute effective trajectories when faced with multiple routes to obtain rewards. We used a computational model to test the informational advantage of the multi-scale representation. A reinforcement learning model involving the hippocampus, entorhinal cortex and striatum learned idiothetic actions based solely on firing rates of multi-scale place and head direction cells. We found that, in a simpler Morris-like maze, the combination of scales is a better source of information for navigational purposes than when taken in isolation. Additionally, larger fields improved learning more than smaller ones when the inactivation experiments were simulated. Results were obtained using computer simulations as well as a mobile robotic platform.

Disclosures: **M. Contreras:** None. **T. Pelc:** None. **M. Llofriu:** None. **A. Weitzenfeld:** None. **J. Fellous:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

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Program#/Poster#: 631.13/BB61

Topic: F.02. Animal Cognition and Behavior

Title: Prefrontal-hippocampal theta coherence, sharp wave ripples, and bursts of cortical unit activity underlie choices and encoding in the radial arm maze

Authors: *M. V. MYROSHNYCHENKO[1], C. LAPISH[2];
[1]Indiana Univ., Indianapolis, IN; [2]Indiana Univ. Purdue Univ. Indianapolis, Indianapolis, IN

Abstract: The radial arm maze (RAM) is a foraging task that is often used to assess executive function guided decision-making. Optimal foraging strategies on this task require the integration of executive and memory systems, which include retrospective and prospective codes. To explore the neural basis of decision-making during RAM performance, the current study acquired multielectrode single-unit and local field potential (LFP) recordings simultaneously in hippocampus (HC) and anterior cingulate (ACC). Initially, rats were presented with four of the eight total maze arms open at once ("training phase"), and the rest of the arms were opened up after the subjects collected the rewards and a one-minute delay was completed ("test phase"). Any arm re-entries were counted as errors, and only trials with one test phase error or less were used in the analysis. ACC unit firing was elevated at choice points and reduced at reward points. Moreover, both ACC and the HC showed elevated theta power shortly prior to the reward point and sharp wave ripples shortly after reward acquisition on correct choices only, which is consistent with findings in other choice tasks. These observations held during test phase and were disrupted during the training phase in ACC, but not the HC. It has been suggested that HC sharp wave ripples contain episodes of replay of visited locations and theta of locations ahead of the animal - information necessary for decision-making using both prospective and retrospective codes. Theta and ripples are present in the HC during both training and test phases, consistent with lesion evidence that hippocampus is necessary for both prospective and retrospective strategies. In ACC, theta and ripples are only present during test phase and not during training phase, which is in line the evidence showing that prefrontal cortex is only necessary for prospective coding. These task phase-dependent observations may help explain how HC and ACC networks integrate information related to prospective and retrospective codes.

Disclosures: M.V. Myroshnychenko: None. **C. Lapish:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: F.02. Animal Cognition and Behavior

Support: NIH T32 ES07051

Title: Egocentric learning deficits in rats produced by developmental manganese overexposure or adulthood 6-hydroxydopamine toxicity are exacerbated in combination

Authors: *R. A. BAILEY, A. GUTIERREZ, R. M. AMOS-KROOHS, C. V. VORHEES, M. T. WILLIAMS;
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Abstract: While manganese (Mn) is an essential nutrient in the human diet, it causes neurotoxicity in excessive doses. In adult humans, manganese overexposure (MnOE) produces gait disturbance, rigidity, bradykinesia, and cognitive deficits. A number of genes involved in Mn homeostasis are also affected in some types of familial Parkinson's disease (PD), however the relationship between these two conditions is poorly understood. In an initial study, Mn (100 mg/kg) was galvaged to Sprague-Dawley rats from postnatal day (P)4 to P28 every other day, and the MnOE animals were studied in a variety of learning and memory tasks. In the Cincinnati Water Maze (CWM), the MnOE animals had longer latencies and more errors than controls, indicating deficits in egocentric learning. These animals also have deficits in spatial learning in the Morris water maze (MWM). Sprague-Dawley rats given 6-hydroxydopamine (6-OHDA) dopaminergic lesions of the neostriatum at a subthreshold dose that is used to model PD also had deficits in egocentric learning. This finding is similar to PD patients, who often have trouble with egocentric navigation. In this study, we combined MnOE with 6-OHDA to investigate if MnOE exacerbates the effects of dopamine lesions. Sprague-Dawley rats were treated with Mn or saline from P4-28 and on P60, were administered 6-OHDA or vehicle into the neostriatum. In a preliminary analysis, animals with Mn and 6-OHDA had longer latencies and more errors than Mn or lesions alone in the CWM. These animals were also tested in the Morris water maze and conditioned fear test, and these data are currently being analyzed to determine if there is an interaction of MnOE and dopamine depletions. The data suggest that Mn may play a role in exacerbating the cognitive symptoms following dopaminergic depletions by sensitizing the animals to a "second hit." Mn may be an environmental factor predisposing to earlier or more severe PD.

Disclosures: R.A. Bailey: None. **A. Gutierrez:** None. **R.M. Amos-Kroohs:** None. **C.V. Vorhees:** None. **M.T. Williams:** None.

Poster

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Topic: F.02. Animal Cognition and Behavior

Support: NSERC

Title: Contextually mediated zenk expression in the hippocampal formation of the male brown-headed cowbird (Molothrus ater)

Authors: *S. L. GRELLA[1], M. F. GUIGUENO[2], D. J. WHITE[1], D. F. SHERRY[3], D. F. MARRONE[1,4];
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Abstract: Background: For many years, researchers have sought to characterize the homology between the hippocampal formation (HF) of birds and mammals, based on the functional conservation of these structures. The mammalian hippocampus creates representations of the surrounding environment by recruiting neuronal ensembles, resulting in the transcription of immediate early genes (IEGs) such as *zif268*. **Method:** We used fluorescent *in-situ* hybridization and confocal microscopy to measure IEG *zenk* (avian orthologue of *zif268*) expression in the HF of male brown-headed cowbirds following exposure either to two different contexts or the same context twice. **Results:** The proportion of cells repeatedly expressing *zenk* was significantly higher in birds that explored the same context twice compared to birds that visited different contexts. **Conclusions:** This suggests that the pattern of *zenk* expression in the avian HF is spatially selective and that cells are recruited to form contextual maps in a similar manner to the mammalian hippocampus. These data are also consistent with findings demonstrating that HF cells in the pigeon show place cell-like patterns of activity.

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Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: F.02. Animal Cognition and Behavior

Title: Neural representations of others' place-related information

Authors: *T. DANJO, S. FUJISAWA;
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Abstract: Observing and understanding others' behavior are critical for animals' survival and social interaction. It has been well demonstrated that mirror neurons that are activated both for particular actions of one's own and other animals play important roles in learning new skills. However, even though some species of animals are capable of understanding others' behavior as a whole and making decisions accordingly, how the overall recognition of others' behavior is represented and processed to make one's decisions has not been well identified. Here, we focus on how the complex information regarding to others' behavior, decisions and positions is represented in the rodent brain. As for the information of the position, it has been well established that pyramidal neurons in the hippocampus represent the place of its own. In contrast, little is known about how animals represent other animals' place and how the cognitive spatial map is related with the representation of others' place. To examine these questions, we designed a behavioral task with a T-maze apparatus for a pair of rats in which one rat has to observe the behavior of the other and decide its choices depending on the observation. We show behavioral results in this task and the electrophysiological data from the hippocampus and prefrontal cortex during the task.

Disclosures: **T. Danjo:** None. **S. Fujisawa:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

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NIH RR00169

Title: Functional reorganization of the medial temporal lobe memory system following neonatal hippocampal damage in monkeys

Authors: *P. LAVENEX[1], L. CHAREYRON[2], L. STICKLEY[2], P. BANTA LAVENEX[1], D. G. AMARAL[3];
[1]Univ. of Lausanne, Lausanne, Switzerland; [2]Univ. of Fribourg, Fribourg, Switzerland; [3]Univ. of California at Davis, Sacramento, CA

Abstract: In humans, the hippocampus is essential for the processing of semantic and episodic memories; damage to this structure in adulthood results in amnesia. However, semantic memory is preserved in subjects who sustained hippocampal damage early in life, suggesting that the medial temporal lobe memory system might undergo structural and functional reorganization after neonatal hippocampal lesion. Similarly, we have previously shown that spatial relational learning is impaired in monkeys who sustained hippocampal lesion during adulthood, whereas spatial relational learning persists in monkeys who sustained hippocampal lesion shortly after birth. Here, we aimed to characterize the structural and functional reorganization of the medial temporal lobe memory system in rhesus macaques following neonatal hippocampal lesion. Shortly before death, animals explored a novel open-field environment in order to activate brain structures involved in spatial learning and memory. We performed quantitative analyses of expression of the immediate-early gene c-fos, a marker of neuronal activation, to determine the brain structures that might enable spatial learning following early hippocampal lesions. The cortical regions known to contribute to spatial memory processing, and which originate most of the afferent inputs to the hippocampal formation, were differentially affected by early hippocampal lesions. In early hippocampal lesioned monkeys, the exploration of a novel environment induced an activation of the parahippocampal and caudal perirhinal cortices, as in control monkeys. In contrast, in lesioned monkeys exploration did not lead to significant activation of the entorhinal, retrosplenial and posterior cingulate cortices, as in control monkeys. Analyses of retrograde tracer injections did not reveal a major structural reorganization of the medial temporal lobe memory system following early hippocampal lesions. We hypothesize that spatial information can be transferred and processed via the perirhinal and parahippocampal cortices, in absence of functional hippocampal circuits. In contrast, the absence of activation of the entorhinal, retrosplenial and cingulate cortices suggests that spatial information processing in these cortical areas might be dependent on proper hippocampal function and output. These results suggest that the functional reorganization that contributes to the preservation of memory function following early hippocampal damage might be characterized by subtle changes in

functional connectivity between cortical areas, which could be sufficient to support allocentric spatial memory formation over repeated trials.

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Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant 5P01AI073693

NIH Grant P01AI102852

Title: Validation of the clockmaze as a robust task for hippocampus-related spatial cognition in mice

Authors: ***P. T. HUERTA**, R. SANKOWSKI, E. GIBSON, C. REY, K. J. CLUNE, T. S. HUERTA, S. ROBBIATI;
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Abstract: Cognitive impairment (CI) is a major risk factor for disability in a variety of clinical conditions. The recent years have shown a tremendous gain in understanding the molecular mechanisms of CI, but the impact of these findings on improving CI remains marginal. This lack of basic-to-clinical translation is puzzling, and it substantially hinders preclinical drug development. Given that mice are highly used in preclinical CI studies, we hypothesize that the intrinsic limitations of the behavioral paradigms applied to mice are a contributing factor to the current status. For example, the Morris watermaze (MWM) remains the most widely used task for hippocampus-related learning although it is notorious for strain bias in mice. Also, hippocampal dysfunction can be masked in MWM if mice apply mixed (spatial, nonspatial) solving strategies. The objective quantification of such strategies is complex and further confounds the interpretation of results. Deacon & Rawlings (Behav. Neurosci. 116, 472-478, 2002) introduced a task in which mice learned to escape from shallow water in a paddling pool. Here we present a large-scale validation of this task, which we have dubbed the clockmaze, as a highly reliable tool to test spatial cognition. The clockmaze is a circular arena equipped with 12 potential exits that are located in the wall of the arena like the numbers on the face of a clock. All

exits are blocked (black plugs) except for one that leads to a small tunnel. Mice learn to escape from the arena, which is filled with 2 cm of water, by using distal cues. We tested 3 strains: C57BL/6 (55 males, 58 females), Balb/Cj (55 males, 50 females) and Swiss (25 males, 25 females). We found that C57BL/6 and Balb/Cj mice learned with similar ease several versions of the task (reference memory, working memory, trials to criterion). We developed a robust algorithm to assess the strategies (spatial, nonspatial, futile) with easily quantifiable readouts. Using pharmacological approaches (n = 37) and genetic disruption of NMDA receptor function (n = 53), we show that the clockmaze relies on the integrity of the hippocampus. We conclude that the task provides a robust assessment of cognitive performance, which will facilitate hypothesis testing and contribute to the global effort to combat CI.

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Poster

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Title: The vestibular contribution to self-motion perception in the behaving mouse

Authors: ***E. BRACEY**[1,2,3], B. PICHLER[3], C. V. ROUSSEAU[3,2], T. MARGRIE[3,2];
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Abstract: Vestibular signals are thought to be critical for the neuronal representation of heading direction and distance travelled. How accurately the vestibular system allows rodents to perceive and discern self-motion information has, however not been quantified. To address this, we designed a go/no-go discrimination paradigm in head-fixed mice that measures perceptual responses to precisely delivered rotational stimuli. Mice were positioned on a rotating platform in a dark, sound-attenuated chamber with their semicircular canals positioned around the rotation axis, then trained to discriminate two 45° horizontal rotations with different peak angular velocities, moving in the same direction with the same stimulus onset and offset times. All mice surpassed 80% accuracy for 100 consecutive trials (criterion) within 3000 repetitions, typically performing 100 - 300 trials per day. Mice were next trained on a go/no-go olfactory task and

achieved high discrimination accuracy for both rotation and odor stimuli (final 200 trials: rotation; 85 ± 1.42 %; odor; 90 ± 1.29 %, n = 6; mean ± SEM). After reaching criterion on both tasks, the left and right posterior and horizontal semicircular canals of three mice were exposed and injected with 5ul kanamycin (500 mg/g b.w.). After recovery, kanamycin-treated mice performed significantly worse on rotation discrimination than sham-treated animals (first 200 rotation trials after treatment: sham; 79.33 ± 1.99%, n = 3 mice vs kanamycin; 64.83 ± 2.61%, n = 3 mice, MWU p value 0.3). Discrimination deficits were not due to loss of licking motor-function, reduced motivation or impaired memory because odor discrimination was unaffected in kanamycin and sham-treated mice (first 200 odor trials post treatment: sham; 82.0 ± 2.75%, n = 3 mice vs kanamycin; 91.67 ± 1.56%). These experiments indicate mice can accurately discriminate horizontal rotations with different velocity profiles - to our knowledge the first direct evidence of a behavioral correlate of egocentric motion-perception in rodents. Reduced discrimination scores after kanamycin treatment suggest this ability relies critically on signals generated in the vestibular apparatus rather than proprioceptive or somatosensory cues. Ongoing work is investigating discrimination limens and detection thresholds for rotational stimuli that will be combined with neuronal recording and opto-genetic manipulation of underlying brain regions involved.

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Poster

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Title: Expanded firing patterns of grid cells in rats climbing on a wall

Authors: *G. CASALI, K. J. JEFFERY;
Exptl. Psychology, UCL, Inst. of Behavioural Neuroscience, UCL, London, United Kingdom

Abstract: Place cells (PCs) are hippocampal neurons whose firing increases when an animal is in one particular region of the environment, producing a focus of activity known as place field. Grid cells (GCs), found one synapse upstream in entorhinal cortex, display multiple evenly spaced place fields. Therefore, in contrast to PCs encoding the animal's current location, GCs process metric information by integrating travelled distances and directions, information likely to be used by the PCs to support navigation. A question of interest is whether GCs and PCs encode vertical space in the same way as horizontal. In a previous study on a pegboard maze(1), we found that GCs did not encode distance in the vertical dimension, producing vertical stripes instead of circular firing fields. However in that experiment, the animals remained horizontally oriented while climbing on the pegs, leading us to propose that GCs might use the plane of locomotion as the reference frame for encoding. In the present experiment we tested this by recording as animals climbed on a wall covered with chicken wire, where their bodies were now oriented vertically. We found that GCs now produced circular firing fields on the wall; however there was an increase in both field size and inter-field distances. PCs had fewer firing fields on the wall than on the floor but their size was unchanged. We then analysed theta, a 7-11 Hz local field potential oscillation that may be important for distance calculations. We found that theta frequency correlated with animal's speed on the wall as well as on the floor but there was a decrease in both the slope and intercept of the regression line, possibly suggesting an altered computation of movement speed on the wall. In conclusion, these results support the hypothesis that body orientation determines the GC and PC frame of reference; additionally, GCs' processing of distances is radically altered in the vertical plane and PCs also show firing changes. The speed/theta-frequency relationship is also affected. Collectively our findings suggest that the plane of locomotion relative to Earth-horizontal affects spatial encoding in three ways: (i) it determines the GC frame of reference, and (ii) it affects the spatial scale of GC firing, and (iii) it affects the relationship between locomotor speed and local field potential oscillations. These findings support the hypothesis that mammalian encoding of space is planar, and also that encoding of the vertical plane has different metric properties from that of the horizontal.
(1)Hayman R, Verriotis MA, Jovalekic A, Fenton AA, Jeffery KJ. (2011) Nat Neurosci. 14(9):1182-8. doi: 10.1038/nn.2892.

Disclosures: G. Casali: None. **K.J. Jeffery:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 631.21/BB69

Topic: F.02. Animal Cognition and Behavior

Title: Selective silencing of medial prefrontal parvalbumin interneurons induces cognitive schizophrenia-like symptoms in mice

Authors: *G. RIEDEL[1], M. WOLOSZYNOWSKA-FRASER[2], B. PLATT[1], B. CROUCH[1]; [1]Univ. Aberdeen, Aberdeen, United Kingdom; [2]Sch. of Med. Sci., Univ. of Aberdeen, Aberdeen, United Kingdom

Abstract: Cognitive impairment is widely recognized as a core component of schizophrenia (SZ) alongside the positive and negative symptoms which form the basis of diagnosis. Despite this recognition very little progress has been made toward cognitive restoration in SZ patients. As cognitive function is considered a prime determinant of quality of life in SZ there is an incentive to understand the neural correlates of cognitive symptoms. Multiple lines of evidence point to dysfunction of parvalbumin positive interneurons (PVIs) in the dorsolateral prefrontal cortex (DLPFC) in SZ patients. As the DLPFC is a key regulator of working memory (WM), the emergent hypothesis therefore is that dorsolateral PVI dysfunction underlies the cognitive symptoms of SZ. To evaluate this hypothesis we generated a prospective mouse model of SZ via selective cell silencing of PVIs in the rodent medial prefrontal cortex (mPFC), the rodent analogue of the human DLPFC. This was achieved by a bilateral intracerebral injection of a novel cre dependent adeno-associated virus (AAV) into the mPFC of mice expressing cre recombinase under the parvalbumin promoter. AAV payload consisted of either green fluorescent protein (GFP) only (control) or in combination with tetanus toxin light chain (TeLC). Cognitive function was assessed using a Barnes maze paradigm incorporating both acquisition and reversal learning with concurrent bilateral recording of local field potentials (LFPs) from the mPFC and the hippocampal CA1. Results demonstrate no significant difference between groups during acquisition learning ($p>0.05$, virus effect, 2-way ANOVA) or in acquisition probe trials ($p>0.05$, 2-tailed t-test). During reversal learning TeLC transfected animals displayed a significantly faster reduction in mean path length ($p<0.001$) and escape latency ($p<0.0001$) than GFP controls (virus effect, 2-way ANOVA). TeLC animals also displayed poor reversal probe performance paradoxically indicating poor reversal learning. An analysis of visuo-spatial search strategies indicated that this difference is entirely explained by a lack of persistent preference for a previously learned target and a greatly reduced use of spatially precise search strategies in TeLC mice. Analysis of LFP recordings during training indicated that this deficit stems from inappropriate modulation of theta range oscillatory activity in the mPFC of TeLC animals. Cumulatively the results indicate that a selective silencing of *only* PVIs in the rodent mPFC alone is sufficient to induce a schizophrenia-like working memory impairment mirroring that observed in the human condition.

Disclosures: **G. Riedel:** None. **M. Woloszynowska-Fraser:** None. **B. Platt:** None. **B. Crouch:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 631.22/BB70

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant R01-MH073689

Title: Flexible spatial learning in rats requires intact hippocampal-prefrontal circuits

Authors: *P. AVIGAN, K. SEIP-CAMMACK, M. L. SHAPIRO;
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Abstract: Adaptive behavior is guided by reward history and updated when contingencies change. Bidirectional interactions between the hippocampus (HIPP) and medial prefrontal cortex (PFC) may contribute to adaptive behavior by integrating new experiences with long-term memory. The present study investigates whether intact PFC/HIPP circuits are required to adapt spatial responses to changing reward contingencies in a constant environment. Rats trained on a serial spatial reversal task were implanted with four cannulae: two bilaterally aimed at PFC (prelimbic/infralimbic regions) and two bilaterally aimed at either dorsal (dHIPP) or ventral (vHIPP) hippocampus. Spatial learning was tested in a plus-shaped maze with two start arms (North, South) and two goal arms (East, West). In each trial, a rat was placed on a pseudorandomized start arm and could find food reward at the end of one of the goal arms. The same goal arm was rewarded on subsequent trials until a rat achieved criterion performance (10 correct trials out of the previous 12 trials). Then, the other goal arm was rewarded until the rat achieved criterion performance. These spatial reversals continued for a total of 64 trials. Microinfusions of the GABAA agonist muscimol were used to transiently inactivate (a) contralateral PFC/HIPP, (b) bilateral PFC, (c) bilateral HIPP or (d) ipsilateral PFC/HIPP. If projections between PFC/HIPP are primarily ipsilateral, and if PFC/HIPP circuits must be intact in order for rats to respond adaptively to changing contingencies in a given environment, then contralateral and bilateral (but not ipsilateral) inactivations should impair rats' ability to learn serial spatial reversals. Bilateral dHIPP and vHIPP inactivation each impaired rats' ability to learn the initial contingency, and different patterns of errors followed inactivation of the two regions. Bilateral PFC inactivation selectively impaired reversal learning but not learning of the initial contingency; rats continued to visit the previously rewarded goal after the first contingency change. Contralateral inactivation of PFC and vHIPP impaired rats' ability to learn the initial contingency whereas contralateral inactivation of PFC and dHIPP had no effect. Thus, learning initial spatial contingencies requires both the dorsal and ventral hippocampus, whereas

adapting to changing contingencies in familiar circumstances requires the PFC and its interactions with vHIPP.

Disclosures: **P. Avigan:** None. **K. Seip-Cammack:** None. **M.L. Shapiro:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 631.23/BB71

Topic: F.02. Animal Cognition and Behavior

Support: supported by Science Foundation Ireland

Title: Neural representation of space and objects in rat anterior claustrum

Authors: ***M. M. JANKOWSKI**, S. M. O'MARA;
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Abstract: The claustrum of the mammalian brain is an anatomically-substantial but largely unexplored and uninvestigated structure. The claustrum has been the subject of a limited degree of speculation regarding its potential functions, however, its physiological role still remains unknown. Among widespread connections with cortical and subcortical areas, claustrum is connected with medial and lateral entorhinal cortices and hippocampus, structures well known for coding of space and its content. In the present study, we investigated the spatial and temporal properties of neurons located in the anterior claustrum in freely-moving rats. Extracellular recordings were performed using 32-channel drivable microelectrode arrays. The spiking activity of neurons was simultaneously coupled with the animal's position in the environment and direction of the head in horizontal plane. Recordings were performed in different environmental conditions including presentation of objects. Our data suggest, unexpectedly, the presence of cells in anterior claustrum that are responsive to the position in space of the animal, to boundaries enclosing the environment and finally to the presence of objects in the environment. This novel claustral signal potentially directly modulates a wide variety of anterior cortical regions. We hypothesise that one of the key functions of the claustrum is to provide dynamic information about body position, boundaries and landmark information, enabling dynamic control of behaviour.

Disclosures: **M.M. Jankowski:** None. **S.M. O'Mara:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: F.02. Animal Cognition and Behavior

Support: College of the Holy Cross Research Funds

Title: Effects of environmental enrichment on anxiety, sensory gating, sociability, and spatial learning in mice

Authors: T. R. HENDERSHOTT, S. LANGELLA, P. S. MCGUINNESS, *A. C. BASU; Psychology, Col. of the Holy Cross, Worcester, MA

Abstract: In 1942 Donald Hebb compared the spatial problem solving ability of rats raised in his home as pets to rats raised in standard laboratory conditions. He found that the pet group showed superior learning ability to the laboratory group. Not only did the pet group initially show better spatial problem solving ability, but the rats in this group also improved more from trial to trial than the laboratory group. This led Hebb to hypothesize that "the richer experience of the pet group during development made them better able to profit from new experiences at maturity." Many researchers have attempted to replicate Hebb's results using laboratory-based environmental enrichment protocols in rodents, however there are three common challenges to interpreting data from these studies: (i) a running wheel is included in the enriched environment, (ii) control animals are raised in isolation rather than standard group housing conditions, (iii) the effects of enriched housing are measured only in mutant animals without wild-type control groups that would allow assessment of enrichment effects alone. We have not included a running wheel as an aspect of our enrichment protocol, and used wild-type animals reared in standard laboratory conditions with cagemates as our control group. In this experiment we compared male and female wild-type C57BL/6J mice reared from weaning age in a standard laboratory environment (SE) to those reared in an enriched environment (EE), using measures of anxiety-like behavior, sensory gating, sociability, and spatial learning and memory. Enriched animals displayed significantly less anxiety-like behaviors and reduced prepulse inhibition. To evaluate spatial learning and memory, we analyzed the latency to escape, path lengths, and search strategies used by the mice in a Morris Water Maze. The search strategies were grouped into either spatially precise (SP) or imprecise (SI). We found that enriched mice displayed enhanced spatial learning.

Disclosures: **T.R. Hendershott:** None. **S. Langella:** None. **P.S. McGuinness:** None. **A.C. Basu:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 631.25/BB73

Topic: F.02. Animal Cognition and Behavior

Title: Effects of different levels of environmental enrichment on reversing cholinergic deficits in rats

Authors: ***E. P. WIERTELAK**[1], D. PALMER[2], J. MEYERS-MANOR[2];
[1]Neurosci. Studies, Macalester Col., Saint Paul, MN; [2]Neurosci. Studies, Macalester Col., SAINT PAUL, MN

Abstract: Previous research has found environmental enrichment (EE) to ameliorate the effects of anti-cholinergic drugs seen to mimic the inhibition of ACh activity found in Alzheimer's patients, as well as positively influence the physical growth of specific neuroanatomical structures in the brain. This study illuminates the importance of different levels of EE in reversing the effects of the anti-cholinergic drug, scopolamine, on a rat's ability to acquire and retain information in the Morris water maze. Rats (10 months old) were housed in groups of two or four (dependent on experimental condition) in three different levels of enrichment: rats in the Standard Enriched Environment (SE) were housed in groups of two in standard, clear, plastic laboratory cages (46cm x 24cm x 21cm); rats in the Moderate Enriched Environment (ME) were housed in the same cages as the SE animals; however, a transparent plastic tube was placed in the cage and corn chips were added daily; rats in the Heavy Enriched Environment (HE) were housed in groups of four in identical larger, wire and plastic cages (64cm x 15.75cm x 32.5cm), with a transparent plastic tube, corn chips, a running wheel, and a ladder to a second level. After being housed under one EE condition for one month, rats were trained to navigate to a hidden platform in the Morris water maze for two days, at twelve trials per day. Half of the rats in each housing condition were given a subcutaneous injection of scopolamine (.6mg/kg), while the remainder received saline (vehicle) solution. The time taken to reach the platform in the Morris water maze was recorded for each rat during each trial. Final analysis examined rat latencies to reach the platform in the last learning trial of the second day. Overall, these data suggest that spatial memory in rats is significantly affected as enrichment increases - where rats in heavier enriched environments learn and process information at a more effective rate than standard

enriched rats in relation to their recorded latencies to reach the platform. Analysis suggests that heavy enriched, scopolamine, rats have lower latencies than standard enriched, scopolamine, rats; furthermore, heavy enriched, scopolamine, rats showed similar latencies to standard enriched, saline, rats. Environmental enrichment may play both a treatment and prevention role by targeting some of the neurological symptoms seen in AD, memory and spatial awareness.

Disclosures: E.P. Wiertelak: None. **D. Palmer:** None. **J. Meyers-Manor:** None.

Poster

631. Cortical and Hippocampal Circuits: Spatial Navigation

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Program#/Poster#: 631.26/BB74

Topic: F.02. Animal Cognition and Behavior

Support: NINDS NS053907

Title: Neural correlates within nucleus prepositus and paragigantocellularis during active and passive movement

Authors: *J. R. DUMONT, S. S. WINTER, K. B. FARNES, J. S. TAUBE;
Psychological Brain Sci., Dartmouth Col., Hanover, NH

Abstract: An animal's perceived sense of orientation depends upon the head direction (HD) system, involving structures primarily along Papez' circuit. However, how the HD signal is generated and maintained remains unclear. Damage to the vestibular system disrupts neural firing within the HD system. Several brainstem nuclei including the nucleus prepositus hypoglossi (NPH) and dorsal paragigantocellularis reticular nuclei (PGRNd) form part of an ascending vestibular pathway to the HD circuit, and may contribute critical neural information utilized for navigation and orientation. Indeed lesions to the NPH severely disrupt HD cells within the anterodorsal thalamic nuclei. To further understand how the NPH and PGRNd may contribute to the HD system, extracellular recordings were made in these areas while rats either freely foraged in a cylindrical environment or were restrained (head-fixed) and passively rotated. During active movement in the cylinder, both of these nuclei contained cells that correlated with changes in the rat's angular head velocity (AHV). Two types of AHV cells were observed: 1) symmetrical AHV cells that increased neural firing with increases in velocity to both clockwise and counterclockwise head rotations; 2) asymmetrical AHV cells, which responded differentially to clockwise and counterclockwise head rotations (e.g., increased responding to increases in velocity in clockwise direction while decreasing in the counterclockwise direction). When rats

were passively rotated, cells in NPH and PGRNd maintained their sensitivity to changes in AHV. In addition to AHV cells, some neurons within PGRNd encoded the position of the rat's head in the pitch plane, similar to those seen before in the lateral mammillary nucleus, where firing increase as the rat pitched its head vertically. These cells perhaps allow the rat to maintain its orientation while traveling along vertical surfaces. These results indicate that spatially modulated neurons exist within brainstem nuclei forming part of an ascending vestibular pathway to the HD circuit, and provide critical information about rotational movement of the rat's head in both the pitch and yaw plane. In addition, the AHV signal is maintained during passive rotation, most likely by vestibular inputs as opposed to proprioceptive/motor efference cues.

Disclosures: **J.R. Dumont:** None. **S.S. Winter:** None. **K.B. Farnes:** None. **J.S. Taube:** None.

Poster

632. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 632.01/BB75

Topic: F.02. Animal Cognition and Behavior

Title: Synchronicity without rhythmicity in the hippocampal formation of behaving bats

Authors: ***T. ELIAV**[1], M. GEVA-SAGIV[1,2], A. FINKELSTEIN[1], M. YARTSEV[1], A. RUBIN[1], L. LAS[1], N. ULANOVSKY[1];
[1]Weizmann Inst. of Sci., Rehovot, Israel; [2]Elsc, Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Hippocampal theta oscillations were proposed to play a key role in multiple cognitive functions, including memory and navigation, as well as in forming the hexagonal firing patterns of grid cells. Previous findings from bats have questioned these proposals, by reporting absence of theta rhythmicity in hippocampal place cells and entorhinal grid cells. However, recent *in-vitro* experiments suggested possible low-frequency (below-theta) subthreshold oscillations in the entorhinal cortex of bats, which could possibly support the same functions. Here we tested this proposal by recording *in-vivo* from interneurons, place-cells and grid-cells, in both crawling and flying bats. We found that none of these cell types exhibited movement-related rhythmic oscillations, neither at theta nor at any frequency - below or above theta. Surprisingly, although the local field potential (LFP) was highly variable in the bat (unlike the periodic theta-rhythmic LFP in rats), many neurons did exhibit locking to the up-swings or down-swings of the LFP. This neural locking to LFP modulations could potentially serve to synchronize hippocampal-entorhinal cell assemblies. These findings support the notion that, across species, normal hippocampal-entorhinal function may require synchronization of cell-assemblies - and this

synchronization could be non-rhythmic as in bats, or rhythmic as in rodents. Finally, we are now examining whether bat neurons exhibit phase precession relative to the phase of the irregular LFP fluctuations; initial analyses indicate that some cells indeed phase-precess - suggesting the possible existence of phase coding without oscillations.

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Poster

632. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 632.02/BB76

Topic: F.02. Animal Cognition and Behavior

Title: 3D grid cells and border cells in flying bats

Authors: ***G. GINOSAR**, A. FINKELSTEIN, A. RUBIN, L. LAS, N. ULANOVSKY; Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Grid cells and border cells are neurons found in the mammalian medial entorhinal cortex and nearby regions. Both of these cell types are thought to be important for navigation and spatial orientation in mammals by encoding animal position and distance as well as environmental geometry in a 2D space. However, although many animals navigate daily through 3D space - including squirrels, bats, dolphins, and monkeys - no studies to date have attempted to characterize the 3D volumetric firing of grid cells or border cells, in any species. To address this, we used Egyptian fruit bats to investigate whether 3D grid cells and 3D border cells exist, and what their firing patterns look like. We have previously found 2D grid cells in bats crawling on a 2D surface, as well as volumetric 3D place cells in freely-flying bats. Here, bats were trained to fly in a large flight room (~6 x 5 x 3 m) in search of randomly-positioned food, while we wirelessly recorded single-neuron activity in several brain regions where 2D grid cells and border cells are known to exist. Results revealed grid-like structures in recorded 3D firing-rate maps, consisting of repetitive blobby firing-fields. The spacing between firing-fields was more variable than in simulated perfect grids, but was substantially less variable than for randomly-distributed fields - suggesting that 3D firing fields of bat entorhinal neurons are repetitively spaced with a specific spatial scale. We also found 3D border cells that fired along the walls or floor of the environment. Taken together, these preliminary results reveal a complex 3D spatial representation in the bat entorhinal cortex.

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Poster

632. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 632.03/BB77

Topic: F.02. Animal Cognition and Behavior

Title: Vectorial representation of goals in the hippocampus of bats

Authors: ***A. SAREL**, A. FINKELSTEIN, L. LAS, N. ULANOVSKY;
Dept. of Neurobio., Weizmann Inst. of Sceince, Rehovot, Israel

Abstract: Navigation, the ability to reach a desired destination, requires knowledge of one's own location as well as the position and direction to the goal. Decades of research have revealed several types of spatially-tuned neurons in the mammalian hippocampal formation - such as place cells, grid cells and head-direction cells - that encode the position and orientation of the animal. However, very little is known about how neural circuits represent the location or direction of goals - which is essential for goal-directed navigation. To investigate how goal-related information is represented in the brain, we trained Egyptian fruit bats to fly towards elevated platforms (defined as 'goals') in search of food reward, while the activity of single neurons from hippocampal area CA1 was recorded. We found a subpopulation of hippocampal neurons that exhibited rather narrow angular tuning to goal-direction. Additionally, some neurons increased their firing-rate when the bat was approaching the goal, reminiscent of approach cells reported in rodents. Taken together, our preliminary results suggest the existence of goal-direction and goal-proximity signals in the bat hippocampus - a vectorial representation that could support goal-directed navigation.

Disclosures: **A. Sarel:** None. **A. Finkelstein:** None. **L. Las:** None. **N. Ulanovsky:** None.

Poster

632. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: F.02. Animal Cognition and Behavior

Support: NSF Grant 1149718

Title: Positional firing properties of the dorsal subiculum in the navigating rat

Authors: *J. M. OLSON, J. K. LI, E. L. TAO, K. TONGPRASEARTH, D. A. NITZ;
Dept. of Cognitive Sci., UCSD, La Jolla, CA

Abstract: By virtue of its ability to encode environmental positions, the hippocampal formation plays a major role in spatial cognition, navigation, and the generation of episodic memories. The dorsal subiculum serves as perhaps the major efferent pathway leaving the hippocampal formation. Yet, the positional firing properties of subicular neurons have not been examined to nearly the same extent as other hippocampal sub-regions. Therefore, to reveal the role of different spatial frames of reference on the discharge of subicular subpopulations, we recorded ensembles of rat subicular neurons during a simple self-guided navigational task. Individual task trials entailed movement through a sequence of three left or right 90-degree turns to one of four potential reward sites. Completion of trials always yielded reward provided that the current path/action sequence was not that of the previous trial. All four paths were of the same length. Two additional 'return' paths along the maze perimeter led the animals back to the starting point for a new trial. Utilizing only uninterrupted path traversals, linearized positional firing rate vectors were constructed for each of the six possible paths (4 main, 2 return) by fitting tracking and spiking data to custom, path-specific templates. With the addition of 90-degree track rotations in some recordings, it was possible to examine subicular activity with respect to movement actions (left versus right turning) and several external/allocentric reference frames (environment, position in specific paths, position in any path). We find that many neurons differentiate the ongoing path being traversed even across segments of the maze common to multiple paths. However, another subset neurons encode analogous portions of two or more pathways, effectively mapping allocentrically different positions according to their commonality in terms of route progression. In addition, a few neurons exhibited activity specific to single positions in the environment, reminiscent of 'place cells' of the CA1 sub-region, while some neurons exhibited orientation-specific tuning. Overall, our results indicate the dorsal subiculum as a region sensitive to position but more closely tied to behavior than the subfields of hippocampus proper.

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Poster

632. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: F.02. Animal Cognition and Behavior

Support: NSF-1149718

DGE-1144086

Title: Route versus environment centered properties in the spatial firing patterns of retrosplenial cortex neurons

Authors: *A. S. ALEXANDER, D. A. NITZ;
UCSD, San Diego, CA

Abstract: Recent work from our laboratory examined the potential role of retrosplenial cortex (RSC) in encoding conjunctions of spatial information of qualitatively different types. RSC neuron ensembles effectively encoded the left versus right turning behavior of rats traversing three-turn sequences along paths through an environment indicating a mapping of spatial information in one or more egocentric frames of reference. The same ensembles contained neurons whose positional rate vectors distinguished positions across the same paths, thereby providing spatial information in a route-based frame of reference above and beyond what could be accounted for by firing correlates to specific actions (e.g., left or right turns). Nevertheless, largely distinct route-position-encoding ensembles were observed when the path occupied different locations within the larger environment. Thus, RSC maps position within complex routes and the position of routes within an environment. In the present work, we further examine the positional firing properties of RSC neurons as animals traversed part or all of the perimeter of a plus shaped track having views to the surrounding recording environment. Full track traversals returned the animal to its starting location after executing a R-L-R-R-L-R-R-L-R-R-L-R turn sequence with 25 cm inter-turn intervals. Half track traversals required the animal to spontaneously stop after completing a R-L-R-R-L-R turn sequence. Half versus full track traversal was dictated by the experimenter's placement of the animal at one of two randomly selected positions on the track at the beginning of each trial. The task design permits assessment of several aspects of RSC: 1) the extent to which RSC ensembles discriminate common portions of two paths having complete overlap in environmental space; 2) the extent to which RSC, as for neighboring posterior parietal cortex, maps recurrence in the shape of path segments; and 3) whether rate vectors for 1/2-path traversals match the first, middle, or last 1/2 of the rate vectors observed across the full path. The latter question further addresses the manner in which RSC ensemble patterns mapping position in routes is related to the larger environmental/allocentric space. Overall, RSC neuronal ensembles did not discriminate portions of the half and full

traversals that overlapped in allocentric space. RSC neurons, did however, discriminate similarly shaped route segments that occurred in distinct allocentric locations. The results indicate that RSC route-referenced activation is dependent upon the allocentric position of the route within the broader environment.

Disclosures: A.S. Alexander: None. **D.A. Nitz:** None.

Poster

632. Cortical and Hippocampal Circuits: Spatial Navigation

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NIH NIMH R01 2R01MH083686-06

Title: A subset of CA1 and subiculum neurons selectively encode rewarded locations

Authors: *J. L. GAUTHIER, D. W. TANK;
Princeton Univ., Princeton, NJ

Abstract: Lesion studies have demonstrated that the hippocampus is critical for the retention of spatial memories, such as the location of an escape platform in a water maze, as well as transferring those memories to other brain areas. However it remains unclear which features of hippocampal physiology convey the memory. Previous studies have shown that when rewards are presented at fixed locations, a higher density of place fields in CA1 develop near the rewards. We set out to distinguish whether this reflects a generally increased density of place fields, or whether the activity of some cells is specifically related to reward. Mice were trained to run on two virtual linear tracks with rewards at several possible locations, and simultaneous optical recordings were made from two major hippocampal output structures, CA1 and the subiculum. Consistent with previous studies, an increased density of place cells was found near rewarded locations. Interestingly, when environmental changes were made that induced either global remapping or rate remapping, the same subset of neurons maintained firing fields near the reward. These observations reveal a previously undescribed feature of hippocampal remapping: a distinct neural population that shifts its firing fields to consistently predict a rewarded location, despite unrelated restructuring of simultaneously recorded place fields. A further trial-by-trial analysis revealed that activity of reward-predicting cells correlated with behavioral anticipation

of reward, raising the possibility that these cells transmit memory of the rewarded location to other brain areas.

Disclosures: **J.L. Gauthier:** None. **D.W. Tank:** None.

Poster

632. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: F.02. Animal Cognition and Behavior

Support: KIST Institutional Program. (2E25540)

Title: Landmark-control over place cells varies within the CA1 pyramidal layer

Authors: ***T. GEILLER**[1], J.-S. CHOI[2], S. ROYER[1];
[1]KIST, Seoul, Korea, Republic of; [2]Korea Univ., Seoul, Korea, Republic of

Abstract: Whether the range of spatial and non-spatial factors controlling hippocampal place cells involves functionally and/or anatomically distinct circuits is largely unknown. A difficulty when examining the impact of particular landmarks on place cell activity in typical recording environments is the abundance and simultaneity of local/distal cues. To circumvent this difficulty, we used a treadmill apparatus, to have mice run multiple times through a series of small objects, while monitoring neuronal activity in CA1 and CA3. Head-restrained mice moved themselves the treadmill belt, onto which objects were fixed. This setting was previously shown to elicit hippocampal firing patterns similar to place fields, and allows a fine control over spatial cues, which are reduced to the few landmarks on the belt. We found a diversity of pyramidal cell types, contrasting in their firing responses to the distinct landmarks, their remapping dynamics, and their localizations along the radial axis of the pyramidal cell layer. We found that a large fraction of cells had their place fields tightly controlled by specific landmarks, mapping positions before and within landmarks, repeating identically for duplicated positions of the same landmarks, and instantly emerging/disappearing when landmarks were added/removed from the belt. Other cells were separable by their distinct remapping dynamics: ‘switching’ cells, initially silent, developed single fields several trials after landmark additions, while ‘drifting’ cells, located in relatively more superficial parts of the CA1 pyramidal layer, exhibited fields that drifted backwards by tens of centimeters. While place cells are often regarded as a single phenomenon, our findings suggest a variety of mechanisms, with specific anatomical organization across CA regions, and within the CA1 pyramidal layer. The existence of OSLV

cells fits quite well the landmark vector hypothesis, where representation of space is achieved via an encoding of distances to discrete landmarks. In return, cells with looser tie to specific landmarks might provide the flexibility for encoding combinations of cues, or representations less dependent on cues, such as prospective cells and episode cells

Disclosures: **T. Geiller:** None. **J. Choi:** None. **S. Royer:** None.

Poster

632. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: F.02. Animal Cognition and Behavior

Support: KIST Institutional Program (2E25540)

Title: Impact of cues on optogenetically identified Mossy cells of the dentate gyrus

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Abstract: While the dentate gyrus (DG) is believed critical for discriminating the contexts, not much is known about its neural correlate. It has been shown that DG neurons activity is more sensitive than CA1 and CA3 to small environmental changes, consistent with its hypothesized role in pattern separation. The dentate gyrus network is composed of several cell types. In particular, excitatory Mossy cells and inhibitory interneurons, located in the hilus, are reciprocally connected with the granule cells, forming a recurrent network whose operations are largely unknown. To investigate the neuronal correlate of different DG cell types, we trained mice to run for water rewards on a treadmill equipped with the long belt (~2 m) enriched with visual-tactile cues. Typically 4 types of objects with contrasting color and texture were used: 1) a 'forest' of ~3 cm high spines made with hot glue, 2) a field of scattered shrink tubes, 3) a field of scattered pieces of Velcro, and 4) a single ~0.8 cm diameter shrink tube. A ~5µl sweet water reward was delivered through a lick port at a specific belt position on every trial. In order to express halorhodopsin in Mossy cells, we injected cre-dependent halorhodopsin expressing virus in DRD2-cre mice. To simultaneously record and deliver light stimuli, we equipped 3 shanks of a 6-shanks silicon probe (Buzsaki64sp) with optical fibers of 15µm diameters, which connect to a yellow laser (561nm). The laser was turned ON in a given portion of the belt, on alternate trials. Among a total of 880 recorded neurons over 11 sessions, we could identify 35 cells with

activity significantly suppressed by the light stimulation and 55 neurons with activity significantly enhanced. Light-suppressed neurons had spike auto-correlogram shapes characteristic of Mossy cells, as previously described (Henze & Buzsaki 2007). On the other hand, light-excited cells discharged more in bursts and had shorter inter-spike intervals. A large fraction of DG neurons exhibited either single or multiple sharp and stable firing fields associated with the objects of the belt. Light-suppressed cells exhibited a larger fraction of multiple firing fields (23%) relative to the light-excited cells (12%). Our results suggest that mossy cells have distinct neuronal properties and exert an overall inhibitory effect on other cell types in DG.

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Poster

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Support: ERC Starting grant (CHIME)

Wellcome Trust (WT098418MA)

Title: How generalizable is rodent hippocampal function across other species? Preliminary hippocampal recordings in the ferret (Mustela putorius)

Authors: S. L. S. DUNN[1], J. BIZLEY[1], *D. A. BENDOR[2];
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Abstract: In rodents, the hippocampus plays a fundamental role in spatial navigation. Lesions to the hippocampus disrupt spatial memory, while hippocampal neurons (place cells) are tuned to an animal's location in its environment. Furthermore, theta oscillations, a 5-12 Hz rhythmic component in the local field potential, are linked to locomotion and play a critical role in numerous hippocampal models of spatial navigation. However, neural coding principles of the hippocampus are based almost exclusively on rodent studies, and it remains an open question which principles can be generalized to other species. Rodents primarily rely on the proximal sensing strategies of sniffing and whisking. Therefore, their sensory world is tied very closely to their current location. In species where distal sensing is more dominant, activity in the hippocampus is not always consistent with the rodent data. For example, 'spatial-view cells'

have been observed in non-human primates, and theta activity is more closely coupled with echolocation rather than locomotion in bats. To further investigate inter-species differences we have started to record hippocampal activity from the ferret (Mustela putorius): a predatory carnivore, which relies predominantly on the distal senses of audition and vision. Here we present a 3D reconstruction of the ferret hippocampus, which was used to guide electrode implantation, and preliminary data recorded from the ferret hippocampus during various behavioural paradigms.

Disclosures: S.L.S. Dunn: None. **J. Bizley:** None. **D.A. Bendor:** None.

Poster

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Collaborative Research Centre (SFB-1134)

Title: Inter-spike intervals reveal functionally distinct cell populations in the medial entorhinal cortex

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Abstract: The superficial layers of the medial entorhinal cortex (MEC) contain spatially selective neurons that are crucial for spatial navigation and memory. These highly specialized neurons include grid cells, border cells, head direction cells and irregular spatially selective cells. In addition, MEC neurons display a large variability in their spike patterns at a millisecond time scale. In this study, we analyzed spike trains of neurons in the MEC superficial layers and found that these cells can be classified in two groups based on their propensity to fire spike doublets at 125-250 Hz. The two groups, labeled ”bursty” and ”non-bursty” neurons, differed in their spike waveforms and interspike interval adaptation but displayed a similar mean firing rate. Grid cell spatial periodicity was more commonly observed in bursty than in non-bursty neurons. In contrast, most neurons with head direction selectivity or that were firing at the border of the

environment were non-bursty neurons. During theta oscillations, both bursty and non-bursty neurons fired preferentially near the end of the descending phase of the cycle, but the spikes of bursty neurons occurred at an earlier phase than those of non-bursty neurons. Finally, analysis of spike-time crosscorrelations between simultaneously recorded neurons suggested that the two cell classes are differentially coupled to fast spiking interneurons: bursty neurons were twice as likely to have excitatory interactions with putative interneurons as non-bursty neurons. These results demonstrate that bursty and non-bursty neurons are differentially integrated in the MEC network and preferentially encode distinct spatial signals.

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Poster

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Support: NIH Grant RO1 MH097130-01A1

Title: Transgenic activation of MEC LII results in similar changes in the firing properties of CA1 place cells across distinct environments

Authors: *C. LYKKEN[1], N. ESTRADA[1], B. KANTER[1], C. KENTROS[2];
[1]Univ. of Oregon, Eugene, OR; [2]Norwegian Univ. of Sci. and Technol., Trondheim, Norway

Abstract: The hippocampus is critical for episodic memory. The spatial component of episodic memory is thought to be encoded by place cells, which fire in specific locations of the environment. Environmental novelty causes place cells to change their firing rate and/or firing location, a process called remapping. Remarkably, there is no discernible relationship between the firing fields of a particular cell in two distinct environments. The medial entorhinal cortex (MEC), the major input to the hippocampus, contains several cell types with spatial receptive fields, including grid, head direction, and border cells. The relationship between upstream MEC neurons and remapping of downstream hippocampal neurons is still unclear. In order to address this question, we used the tTA-tetO system to express an hM3Dq DREADD (Designer Receptors Exclusively Activated by Designer Drugs) in MEC layer II. The hM3Dq is a modified muscarinic G-protein coupled receptor exclusively activated by an otherwise inert ligand, clozapine-N-oxide (CNO). Previous electrophysiological recordings in our lab demonstrated that systemic injection of CNO increases the firing rate of neurons in layer II of the MEC and causes

grid fields to expand without changing the grid vertices. However, CNO-induced activation of MEC LII neurons produces drastic changes in CA1 place fields ("artificial remapping") in downstream CA1 pyramidal neurons. Multiple transgenic activations of the same entorhinal inputs via multiple CNO injections leads to the same hippocampal network response, suggesting that artificial remapping may be a hard-wired network response. To investigate whether transgenic activation of the same set of MEC LII neurons has a similar effect on two distinct receptive fields of the same CA1 place cell, we recorded activity in CA1 while mice explored two distinct environments before and after the administration of CNO. Since place cells remap between environments, any similarities between two artificial remappings of the same place cell reveal the effects of the same network manipulation on two distinct CA1 receptive fields. In contrast to remapping induced by changes in the animal's experience, our preliminary results suggest that there is a discernible relationship between firing rate changes in distinct environments following transgenic activation of MEC LII. These results not only provide further support for the idea that artificial remapping in response to transgenic activation of MEC LII is a hard-wired network response, but also raise the question of how known changes in input are interpreted by the hippocampal-entorhinal network.

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Title: Transgenic activation of medial entorhinal cortex similarly alters spatial firing properties of CA3 and CA1 place cells

Authors: *B. R. KANTER[1], T.-T. P. NGUYEN[1], C. G. KENTROS[2];
[1]Univ. of Oregon, Eugene, OR; [2]Norwegian Univ. of Sci. and Technol., Trondheim, Norway

Abstract: The hippocampus is required for the encoding of episodic memory, the recollection of "what" happened, "when" it happened, and "where" it happened. Hippocampal place cells are preferentially active as an animal passes through specific locations (i.e. place fields) of a particular environment. When introduced to a novel environment, the firing rate and/or location of place fields drastically change, a process called remapping. Exactly how place cells remap

remains one of the most elusive questions in our field. Our laboratory uses a transgenic mouse line expressing a mutated human muscarinic glutamate receptor (the hM3Dq DREADD) primarily in medial entorhinal cortex layer II (MECII), one of the main inputs to the hippocampus. Systemic injection of clozapine N-oxide (CNO), which only binds to hM3Dq receptors, depolarizes a subset of MECII neurons. We have previously shown that this leads to "artificial remapping" of CA1 place cells, where cells remap though the animal remains in a stable environment. Here, we show that artificial remapping is also induced in CA3 place cells. CA3 has unique recurrent connectivity and responds differently than CA1 to environmental change. Therefore, it has been proposed that CA3 may nonlinearly transform sensory input to support the complementary functions of pattern completion and pattern separation (Guzowski et al., 2004). The authors predict that relative to those of CA1, the firing properties of CA3 will change less with small changes to the environment, but will change more with large changes to the environment. We therefore hypothesized that dose-response curves measuring changes in spatial firing properties at different doses of CNO would differ between CA3 and CA1. To test this hypothesis, we injected a range of doses of CNO to simulate varying amounts of contextual change while recording from CA3 and CA1 place cells. We computed spatial correlations between rate maps of a given cell before and after CNO injection to assess the degree of remapping. Surprisingly, the dose-response curves for the two regions are quite similar. Rather than disproving the model, our results may highlight the mechanistic differences between artificial and traditional remapping. By altering the firing rate of entorhinal inputs in a stable environment, we dissociate an animal's sensory experience and the evoked neural activity to address what truly causes a place cell to remap.

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Poster

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Title: Long-term refinement of CA1 ensemble representations of associations between reward and spatial location

Authors: *E. OTTO HAMEL, M. C. LARKIN, L. J. KITCH, M. J. SCHNITZER;
Stanford Univ., Stanford, CA

Abstract: Memories of rewarding episodes generally last longer than memories of neutral events. The mammalian hippocampus is essential for the formation of episodic memory, but how it preferentially retains memory of rewarding events is poorly understood. In hippocampal area CA1, pyramidal cells exhibit place fields at a higher prevalence around reward and goal locations. However, it has been unknown how CA1 representations of rewarding experiences evolve over the course of learning and whether place fields encoding rewarded locations are more stable than others over the long term. To examine these issues, we used a head-mounted miniature fluorescence microscope to track the calcium dynamics of >10,000 CA1 pyramidal cells (10 mice) expressing the calcium indicator GCaMP6m as the mice learned to perform a reward-motivated spatial task over 9 days. As the mice learned the association between place and reward, there was a progressive refinement of the CA1 neurons' place fields that gradually resulted in a greater preponderance of place fields at rewarded locations. When we altered the spatial profile of reward contingencies, the CA1 representation of space shifted to reflect the new reward sites. The bulk of these changes in the ensemble code arose from cells that had previously been silent or non-coding. Even after the mice learned the new contingencies, the refinement of the neural code continued for multiple days. However, once cells participated in the ensemble representation of space, those encoding a rewarded location were no more likely to persist, re-map, or exit the coding population than other coding cells. Overall, our study reveals key aspects of how CA1 hippocampal codes evolve over days to reflect rewarding experiences and emphasizes the role of cells that are initially silent or non-participants in the coding ensemble.

Disclosures: E. Otto Hamel: None. **M.C. Larkin:** None. **L.J. Kitch:** None. **M.J. Schnitzer:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inscopix, Inc.. F. Consulting Fees (e.g., advisory boards); Inscopix, Inc..

Poster

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Title: Presence of significant directional modulation in rodent hippocampus, in real and virtual environments

Authors: *Z. M. AGHAJAN[1,2,3,4], L. ACHARYA[1,2,3,5], J. MOORE[1,2,3,6], C. VUONG[1,2,3,4], M. R. MEHTA[1,2,3,4,7];
[1]W. M. Keck Ctr. for Neurophysics, [2]Integrative Ctr. for Learning and Memory, [3]Brain Res. Inst., [4]Physics and Astronomy, [5]Biomed. Engin. Interdepartmental Program, [6]Neurosci. Interdepartmental Program, [7]Neurol. and Neurobio., UCLA, Los Angeles, CA

Abstract: Place cells in the hippocampus provide a cognitive map of space in that they fire in a spatially localized manner. These spatial firing properties have been extensively studied and shown to be modulated by multisensory inputs. However, the existence of and mechanisms underlying directional selectivity of place cells have been largely debated[1]. While it is widely accepted that directionality exists on linear paths, the reports on its presence during random foraging have reached conflicting conclusions. Further, the observed directional selectivity has been attributed to vestibular-based self-motion signal in some studies and to distal visual cues in others. These contradictions can arise in part because the traditional analysis methods cannot account for spiking activity modulated by multiple covariates, as is the case for place cells. Additionally, the sources of angular information, namely vestibular and visual cues, are always in register in real word (RW) environments under normal conditions and hence their contributions to directional selectivity are confounded. To address these issues, we first used a generalized linear model (GLM) framework to obtain the underlying directional modulation of hippocampal neurons in RW during a random foraging task. This estimate was independent of the neurons' spatial modulation and unaffected by the behavioral biases within the place fields. Moreover, we used a virtual reality (VR) setup that allowed us to isolate the contribution of visual cues to directional selectivity while keeping the vestibular signal minimal. By utilizing the GLM method, we found that 25% of neurons exhibited significant directional modulation in RW. Surprisingly, a similar level of directional modulation was found in VR demonstrating that visual cues alone are sufficient to elicit directional tuning and that vestibular cues are not necessary[2]. Taken together, these results challenge the commonly held beliefs about rodent hippocampal directional responses. The presence of intact directional selectivity despite impaired spatial selectivity in VR[3] suggests a dissociation between the mechanisms of the two and is reminiscent of the results observed in human and non-human primates. 1. Muller, R., Bostock, E., Taube, J. & Kubie, J. On the directional firing properties of hippocampal place cells. *J. Neurosci.* **14,** 7235-7251 (1994). 2. Acharya, L., M. Aghajan, Z., Vuong, C., Moore, J. & Mehta, M. Visual cues determine hippocampal directional selectivity. *bioRxiv* (2015). doi:10.1101/017210 3. Aghajan, Z. M. *et al.* Impaired spatial selectivity and intact phase precession in two-dimensional virtual reality. *Nat. Neurosci.* **18,** 121-128 (2014).

Disclosures: **Z. M. Aghajan:** None. **L. Acharya:** None. **J. Moore:** None. **C. Vuong:** None. **M.R. Mehta:** None.

Poster

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W. M. Keck Foundation

Title: Causal role of visual cues in determining hippocampal directional responses at single neuron and ensemble level

Authors: *L. ACHARYA[1,2,3], Z. M. AGHAJAN[1,2,4], C. VUONG[1,2,4], J. J. MOORE[1,2,5], M. MEHTA[1,2,4,5,6];
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Abstract: Hippocampal pyramidal neurons encode both position and direction. In rodents the latter has so far been observed only on linear tracks and it is thought the firing properties of place cells are not influenced by the animal's head direction in two-dimensional environments. However, there have been a few, albeit conflicting, reports of directional selectivity in two-dimensional arenas in rats, bats and monkeys. In addition to the inconsistency between one- and two-dimensional tasks, the sensory mechanisms behind this activity remain ambiguous. We recorded CA1 neuronal activity from rats performing a random foraging task in both real world (RW) and virtual reality (VR) two-dimensional arenas with visually distinct walls[1]. About a quarter of neurons in both worlds exhibited significant head-directional modulation, which is comparable to the fraction observed in the head direction system. Since in VR, visual cues are the only reliable spatially and directionally informative cues, and vestibular cues are diminished, this result suggested visual inputs can directly modulate hippocampal activity. To test this hypothesis, we ran rats in four different VR arenas, each with a different amount of angular information. In two, visual cues provided no angular information and had either angularly symmetric visual cues or no walls. Under these conditions no significant directional tuning was

observed. Directional tuning was revived in the second set of arenas that had a single polarizing visual cue that either occupied 90° or 10° of the visual field. Here, the fraction of neurons exhibiting significant directional modulation increased with polarization of the visual cue. These stark differences were not only observed at the individual neuronal level, but also at the level of the ensemble. While there was no directional bias of the ensemble of neurons with significant directional tuning in the rich RW and VR environments, there was a significant ensemble bias towards the sole visual cue in the environments with polarizing cues. Moreover, the magnitude of bias also increased with polarization of the cue[2]. These results show that visual cues are not only sufficient to generate directional modulation of rodent hippocampal neurons but also play a causal role in driving activity at both the neuronal and population levels. They also bridge the gap between rodent and primate studies where hippocampal neurons are responsive to visual scenes. 1.Aghajan, Z. M. *et al.* Impaired spatial selectivity and intact phase precession in two-dimensional virtual reality. *Nat. Neurosci.* 4-6 (2014) 2.Acharya, L., *et al*. Visual cues determine hippocampal directional selectivity. *bioRxiv* 15-17 (2015)

Disclosures: **L. Acharya:** None. **Z. M. Aghajan:** None. **C. Vuong:** None. **J.J. Moore:** None. **M. Mehta:** None.

Poster

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Title: Hippocampal neural dynamics in a virtual Morris water maze navigation task

Authors: *J. J. MOORE[1,2,3,4], L. ACHARYA[1,2,3,5], J. D. CUSHMAN[6,3], C. VUONG[1,2,3,7], Z. M. AGHAJAN[1,2,3,7], B. POPENEY[8], M. R. MEHTA[1,2,3,7,9];
[1]W. M. Keck Ctr. For Neurophysics, Los Angeles, CA; [2]Integrative Ctr. for Learning and Memory, [3]Brain Res. Inst., [4]Neurosci. Interdepartmental Program, [5]Biomed. Engin. Interdepartmental Program, [6]Dept. of Psychology, [7]Dept. of Physics and Astronomy, [8]Dept. of Radiation Oncology, [9]Dept. of Neurology, Dept. of Neurobio., UCLA, Los Angeles, CA

Abstract: It is commonly believed that a stable cognitive map of space is necessary for the successful execution of any navigation task. Indeed, removal of the hippocampus, which contains place cells thought to underlie the cognitive map, impairs performance in the Morris Water Maze task, suggesting a crucial role of hippocampal activity in this task. However, it is unclear if this also means that hippocampal *spatial selectivity* is required for successful execution of this landmark-based spatial navigation task. Recent results from rodents exploring environments in virtual reality (VR) raise questions about this requirement. We recently demonstrated that while rat hippocampal neurons show robust spatial selectivity during random foraging in the real world, spatial selectivity is impaired when body-fixed rats perform the same task in a two-dimensional virtual reality environment (1). Instead, neural responses showed selectivity to distance traveled along systematic paths (1,2). The impaired spatial selectivity could possibly stem from the rats not paying attention to the visual cues during random foraging. Interestingly, rats are able to quickly learn to solve a virtual Morris Water Maze task, where they must pay attention to the visual cues, using the exact same apparatus (3). What, then, is the nature of hippocampal neuronal dynamics during this virtual navigation task? To address this question, we measured neural responses from the dorsal hippocampus while the rats executed the virtual navigation task. Eats were placed on a 2m diameter virtual platform within a 3x3m virtual room with distinct visual cues on the walls. The rats had to find a predetermined, unmarked location on the virtual platform to receive liquid rewards. Rats quickly learned this task. Upon successful learning of the task rats were implanted with multi-tetrode hyperdrives and single unit responses were measured from the dorsal hippocampus. Here we quantify the properties of neural responses in this task and their relation to behavioral performance in this navigational task. This is the first measurement of hippocampal neural responses during a navigation task in a purely visual virtual reality, which can lead to a substantial advance in our understanding of the neural mechanisms underlying navigation. 1. Aghajan, Z. M. *et al.* Impaired spatial selectivity and intact phase precession in two-dimensional virtual reality. *Nat. Neurosci.* (2014). 2. Ravassard, P. *et al.* Multisensory control of hippocampal spatiotemporal selectivity. *Science* **340,** 1342-6 (2013). 3.Cushman, J. D. *et al.* Multisensory Control of Multimodal Behavior: Do the Legs Know What the Tongue Is Doing? *PLoS One* **8,** e80465 (2013).

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Poster

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NIMH (D.F.)

Title: Motivation and validation of an EEG-based estimate of hippocampal replay content

Authors: *C. M. ALTIMUS[1], R. E. AMBROSE[2], B. E. PFEIFFER[3], J. B. HARROLD[2], D. J. FOSTER[2];
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Abstract: Pyramidal cells in the hippocampus, known as place cells, fire robustly in a location specific manner, but also fire in temporally compressed sequences known as replay that can reflect remembered past or planned future behavioral trajectories through the environment. Previously we have introduced a novel and rapid assay using only the local hippocampal electroencephalogram (EEG) that can infer properties of replay sequences without the technically challenging requirement of simultaneously recording large numbers of single units. Here we addressed the question of how the new assay compares to direct measurement of replay sequences, in animals for which both kinds of measurement were taken. We recorded from large numbers of hippocampal place cells simultaneously in freely moving rats, together with local hippocampal EEG. First, we investigated the dependence of accurate replay sequence estimation on the numbers of simultaneously recorded single units, by subsampling cells from the original recorded population. Whereas the position of an animal during spatial exploration can be estimated with high accuracy from as few as 25 cells, the accuracy of replay sequences degraded rapidly as the cell count dropped below 100. At 50 cells, decoded replay sequences showed dramatic changes compared to the original sequences, often with erroneous estimation of the trajectory path. Thus, we find strong motivation for an EEG assay of replay for use in smaller recording preparations such as freely moving mice. Second, in order to validate our novel EEG measure, we compared it directly to replay sequences. We find that as hypothesized the duration of sharp-wave ripple (SWR) events correlates positively with the decoded trajectory length of replay events. Thus replay, that has been reported previously based on a subsampling of the hippocampal cell population and a subset of population spiking events, was found to correlate with a global measure of hippocampal neural activity, the duration of hippocampal SWRs.

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Poster

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Title: Local and distant input controlling excitation in layer II of the medial entorhinal cortex

Authors: *R. PINNA[1], E. C. FUCHS[2], A. NEITZ[2], S. MELZER[2,3], O. TOADER[2], A. CAPUTI[2], H. MONYER[2];
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Abstract: Layer II (LII) of the medial entorhinal cortex (MEC) comprises grid cells that support spatial navigation. The unique firing pattern of grid cells might be explained by attractor dynamics in a network, which requires either direct excitatory connectivity between phase-specific grid cells or indirect coupling via spatially tuned interneurons. However, neither scenario has strong experimental support. Based on electrophysiological and morphological criteria, we identified in LII MEC four types of excitatory neurons that exhibit a cell type-specific local connectivity. Using retrograde and anterograde labeling technique and optogenetic stimulation, we provide evidence that LIII pyramidal cells excite both ipsilateral and contralateral LII neurons. We injected the adeno-associated virus CaMKIIa-ChR2-mCherry in the MEC and stimulated the projecting axons with blue laser light in the contralateral MEC. Employing the same techniques, we demonstrate that the medial septum controls excitation via long-range GABAergic neurons that target preferentially fast-spiking interneurons in LII thereby disinhibiting local circuits. We thus identified local excitatory recurrent connections that could support attractor dynamics and external inputs that likely govern local excitation in LII. The functions of the different cell types *in vivo* remain to be established.

Disclosures: **R. Pinna:** None. **E.C. Fuchs:** None. **A. Neitz:** None. **S. Melzer:** None. **O. Toader:** None. **A. Caputi:** None. **H. Monyer:** None.

Poster

632. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 632.19/BB93

Topic: F.02. Animal Cognition and Behavior

Support: DHHS/NIH/NIMH/IRP

Title: Intact allocentric spatial memory during virtual navigation in rhesus monkeys with bilateral hippocampal lesions

Authors: *B. M. STEEMERS[1], R. SAUNDERS[1], M. MISHKIN[1], C. DOELLER[2], S. GUDERIAN[1];
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Abstract: The hippocampus has been implicated in allocentric spatial memory in rodents, non-human primates, and humans. However, the majority of rodent studies employed tasks that involve a navigational component in a three dimensional environment, whereas the majority of studies in primates did not require navigation, thus rendering the translation of findings from rodents to primates difficult. In the present experiment, we investigated the effect of hippocampal lesions on allocentric spatial navigational memory in rhesus monkeys using a virtual environment. The task, a variant of the Morris Water Maze, which has been used extensively to test navigational spatial memory in rodents, required monkeys to use a joystick to navigate to a rewarded location within a circular arena. This circular arena resided in a larger hexagonal room, with six unique images on the walls of the room providing cues for orientation. No navigational cues were present within the circular arena. The orientation cues, as well as the rewarded location within the arena, were different on each testing day, thus providing a different allocentric spatial memory problem in each session. On each trial, monkeys started navigating from a random location within the circular arena. Performance was assessed as the ratio between the distance traveled (DT) and the optimal distance (OD), given each trial's starting location (perfect performance thus being 1). Preoperatively, monkeys were able to reliably reach a DT/OD ratio of around 1.5 and learned to locate the reward within 20-30 trials. Critically, neither learning rate early in the session nor ceiling performance was significantly reduced after bilateral neurotoxic lesions of the hippocampus. Furthermore, neither performance as a function of proximity of the reward location to the arena wall nor performance as a function of proximity of the starting location to the reward location was decreased after hippocampal lesions. The results

suggest that, in rhesus monkeys, the integrity of the hippocampus is not critical for memory-based allocentric spatial navigation in a virtual reality environment.

Disclosures: **B.M. Steemers:** None. **R. Saunders:** None. **M. Mishkin:** None. **C. Doeller:** None. **S. Guderian:** None.

Poster

632. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 632.20/CC1

Topic: F.02. Animal Cognition and Behavior

Title: Quantifying and exploring the emergence of the late members of the active set of hippocampal place cells in novel environments

Authors: *S. E. FOX[1], J. BARRY[2], K. BOLDING[3];
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Abstract: Hill (1978) reported that for 2 of 12 place cells recorded on a novel T-maze, the place field required up to 10 min to develop. Frank, et al. (2004) showed that such late-onset place fields, absent for minutes, develop abruptly (within < 15 s) on novel arms of T-mazes. Monaco, et al. (2014) identified a relationship between head-scanning and the sudden onset of late-developing place fields in double cue-rotation and novel closed-loop tracks. Temporal Categories. We recorded place cells in environments where rats foraged for pellets on 2-D surfaces and separated the cells into 3 groups by field onset time. We defined “early cells” as those that had a place field (9 edge-contiguous pixels with firing rate > 0) in the first 2 min of a recording session. The onset times of late-developing place fields were bimodally distributed. Place cells that developed a field 2-8 min (3.2 ± 0.3) into a session were defined as “common late cells”; these occurred in both familiar and novel environments and comprised about 15%-20% of the total population of place cells. “Novel late cells” developed a place field between 8 and 16 min (9.3 ± 0.4) and appeared only in environments sufficiently novel to trigger global remapping, where they then comprised 20-30% of the total stabilized place cell population. Disinhibition. For locations outside the fully developed place field of both common and novel late cells, the firing rates before and after onset of rapid in-field firing were similar, so disinhibition seems an unlikely cause for the late-onset firing. Theta Rhythm. After septal injections of gabazine that nearly eliminated theta, 8 late place cells were recorded and all

developed fields in 10 min or less (4.5 ± 1.0). The distribution of these field onset times did not differ from that of common late cells (p_{log} = .23), suggesting that theta oscillations may contribute to the development of firing in novel late cells. Edge Fields. Among early cells, 8 of 50 (16%) had concave place fields at the edge of a novel circular chamber, suggesting they are driven by border cell inputs. A similar fraction (3 of 23, 13%) of such fields occurred among common late cells, but no novel late cells had concave edge fields (0 of 20, binom p = .03 re: early cells). NMDA. Re-analysis of recordings in novel environments after systemic CPP (Kentros, et al., 1998) showed only common late cells, no novel late cells. That may have occurred because place field development in novel late cells requires NMDA, but it also may have occurred because after CPP, thigmotaxis was so pronounced that all cells with late-developing fields were concave edge cells. The CPP-treated rats rarely visited the regions where the fields of novel late cells develop.

Disclosures: **S.E. Fox:** None. **J. Barry:** None. **K. Bolding:** None.

Poster

632. Cortical and Hippocampal Circuits: Spatial Navigation

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Program#/Poster#: 632.21/CC2

Topic: F.02. Animal Cognition and Behavior

Support: NIH Grant R-37NS081242-02

Title: Visual cue-related activity of MEC cells during navigation in virtual reality

Authors: *A. A. KINKHABWALA[1,2], D. ARONOV[1,2], D. W. TANK[1,2];
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Abstract: Previous studies have found distinguishing features for the spatial and orientation tuning of cells in MEC (Medial Entorhinal Cortex), such as the triangular lattice of firing fields of grid cells, the orientation tuning of head direction cells, and the boundary-related activity patterns of border cells. These features were initially revealed by analysis of chronic electrode recordings performed in rodents while they foraged in an open arena. We complemented real arena recordings with navigation along virtual tracks containing a set of landmarks. In this setup, allocentric information experienced by the subject could be more precisely quantified to better understand the type of information represented by the spiking of cells in MEC. Tetrode recordings were obtained in the MEC of mice navigating in both real and virtual environments. We found a striking spatial firing pattern for a subset of recorded cells: firing fields were present

only near the set of cue locations in the virtual environment. To quantify this feature of the spatial firing rate, a cue score was developed. We first defined a ‘cue template’ (1 at cue locations; 0 otherwise) to identify where visual cues were located along the virtual track. We then calculated the maximal cross correlation between the cue template and the firing rate for different spatial offsets of firing field and template. Cells were defined as cue cells if their cue score exceeded a threshold calculated by a bootstrapping procedure using spike shuffled data. We next asked how cue cells respond when cues are removed and found that firing fields were no longer present in the regions where cues were missing. Using activity recorded during foraging in a real arena, the grid, border, and head direction scores for all units were calculated. A large fraction of cue cells had spatially stable firing patterns in the real environment. Some cue cells were conjunctive with border (17%) or grid (11%) cell types, and many of these cells had a significant head direction score during foraging in real arenas (60%). We conjecture that cue cells may play a role in error correction of grid cell spatial firing patterns.

Disclosures: **A.A. Kinkhabwala:** None. **D. Aronov:** None. **D.W. Tank:** None.

Poster

632. Cortical and Hippocampal Circuits: Spatial Navigation

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 632.22/CC3

Topic: F.02. Animal Cognition and Behavior

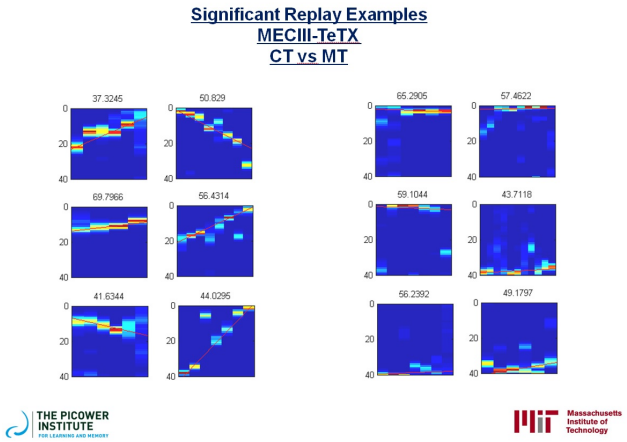
Support: RIKEN - MIT Center Grant

Title: Direct input from MECIII to hippocampal CA1 is crucial for long-range "active" replay during wake but not during sleep

Authors: *J. YAMAMOTO, J. SUH, S. TONEGAWA;
PILM, MIT, Cambridge, MA

Abstract: Hippocampal replay has been suggested to play an important role in spatial navigation, learning an environment, and future path planning. The major input from CA3 to CA1 is considered to be providing mnemonic information for CA1 to re-express temporally structured sequences of recent spatial experiences. However, the functional role of the direct inputs from MEC layer III to CA1 with regard to hippocampal replay remains unknown. In this study, we recorded a large number of CA1 units in MECIII-TeTX transgenic mice with blocked transmission from MECIII to CA1, and their control littermates. We applied a Bayesian Poisson position reconstruction method to decode CA1 unit activities while animals traversed a linear

track. As has been previously reported, we found no major differences in place cell quality, including sharp-wave ripples between these genotypes. However, we found that spatial coverage of replays during quiet wakefulness was significantly shorter (15-30% of 1.5 m linear track) in mutants than in controls (70-90%) during quiet-awake replays; Individual place cells tended to fire longer in mutants to result in comparable sharp-wave ripple duration between groups (50-150 ms). Both impaired and normal replay events mostly started from the animal's current location. We then examined replay events during subsequent sleep. Surprisingly, we found no differences in the coverage of replays during sleep in both genotypes. CA1 units in mutants could re-express a comparable length of the track (70-90%) suggesting that replay during quiet awake versus sleep may be governed by different hippocampal circuits. Quiet awake replays during spatial navigation tasks have been suggested to reflect an animal's "active" future path planning; Our results support the idea that the direct input from MECIII to CA1 may play a crucial role in "active" memory retrieval rather than "passive" memory replay.



Disclosures: **J. Yamamoto:** None. **J. Suh:** None. **S. Tonegawa:** None.

Poster

632. Cortical and Hippocampal Circuits: Spatial Navigation

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Topic: F.02. Animal Cognition and Behavior

Support: National Agency for Research ANR-REG-071220-01-01

Fondation pour la Recherche Médicale DEQ20120323730

Title: Contribution of cerebellar Parallel Fiber-Purkinje Cell LTP to hippocampal spatial map stability

Authors: *J. M. LEFORT[1], F. JARLIER[2,3,4], C. I. DE ZEEUW[5,6], L. RONDI-REIG[2,3,4], C. ROCHEFORT[2,3,4];
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Abstract: Several plasticity sites have been described in the cerebellar cortex, among which the Parallel Fiber-Purkinje Cell synapse, displaying both Long Term Depression (LTD) and Long Term Potentiation (LTP), has received most interest. We previously showed that a lack of PF-PC LTD altered self-motion processing and subsequent dependent hippocampal processes, i.e. maintaining a cognitive representation of space using self-motion information and using it for optimal goal-directed behavior. However, it remains unclear if these navigation processes specifically depend on cerebellar LTD per se or ensue from a general disruption of cerebellar circuitry. To test this we investigated the functional consequences of a deficit of LTP at PF-PC synapses using L7-PP2B mice model. Hippocampal place cell properties of L7-PP2B mice were characterized during free exploration of a circular arena. In contrast to mice lacking cerebellar LTD, place cell properties of L7-PP2B mice were not impaired when mice had to rely on self-motion cues. Surprisingly, L7-PP2B place cells displayed instability in the absence of any proximal cue manipulation in 20 % of the recording sessions, characterized by a coherent angular rotation of the whole set of recorded place cells. During these events, in which the spatial relationships between the object and the mouse spatial representation are changed, mice displayed an increased exploration of the object, suggesting that for the mouse the object was located at a new position. These data suggest that, in the absence of cerebellar LTP, hippocampal spatial representation cannot be reliably anchored to the prominent external cue. These results along with those from L7-PKCI mice, indicate that the cerebellum might be involved in multiple sensory processing required to navigate properly.

Disclosures: J.M. Lefort: None. **F. Jarlier:** None. **C.I. De Zeeuw:** None. **L. Rondi-reig:** None. **C. Rochefort:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 633.01/CC5

Topic: F.02. Animal Cognition and Behavior

Support: F. Hoffmann-La Roche Ltd

Title: Assessing reward learning in macaques using a probabilistic selection task

Authors: *C. GLAVIS-BLOOM[1], D. ALBERATI[2], T. BALLARD[2], M. CROXALL[3], K. TAYLOR[2], D. UMBRICHT[2], T. L. WALLACE[1];
[1]SRI Intl., Menlo Park, CA; [2]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [3]Lafayette Instrument Co., Lafayette, IN

Abstract: The Probabilistic Selection Task (PST) is a paradigm that evaluates whether subjects learn better from positive or negative outcomes of probability-related choice behavior mediated through cortical-striatal dopaminergic pathways. The PST has been utilized to evaluate several neuropsychiatric and neurodegenerative disorders, and has revealed reward-related learning impairments in selected patient populations (e.g, schizophrenia, autism). The intent of our studies was to assess probabilistic reward learning in non-human primates (NHPs) for evaluating potential novel therapeutics in a species with close homology to humans. Eight adult male Cynomolgus macaques were trained initially on a 1- and then 3-pair concurrent discrimination (CD) task in which selection of one stimulus in a pair resulted in delivery of a food reward 100% of the time (100 trials/session). The animals had to identify which stimulus in the pair was associated with the reward and reliably select it with ≥ 80% accuracy for ≥ 2 test sessions before moving to the next level of training. Stimulus pairs were novel in each test session and presented first as blocked then randomized trials. Animals acquired the rules of the CD task quickly and reached proficiency at each level within 5 test sessions. Following CD training, animals began PST training, modeled after the work of Waltz et al., 2007 (Biol Psych 62;756-64). For this task, animals were presented with 3 unique stimulus pairs (A/B; C/D; E/F) in each session, each rewarded with a different probability (A-80%/B-20%; C-70%/D-30%; E-60%/F-40%). On each trial, the NHPs made a two-alternative forced choice and learned to choose the most frequently rewarded stimulus from each set based on the identified probabilities. Animals received blocks of 60 trials of pseudo-randomized presentations of the pairs until 1) they met the criterion of selecting ‘A’ 65% of the time, ‘C’ 60% of the time, and ‘E’ 50% of the time, or 2) they had completed 6 blocks of trials (360 trials, 120 of each pair). Once animals reliably met the performance criterion, the transfer test, consisting of novel combinations of stimuli, was introduced to test whether NHPs learn better from positive (rewarded, i.e., A/C; A/D; A/E; A/F) or negative (non-rewarded, i.e., B/C; B/D; B/E; B/F) events. Our early results indicate macaques readily learn the PST through a combination of positive and negative events, with evidence of learning being driven more consistently through positive feedback, in line with the observed behavior in healthy subjects. The PST in macaques may serve as a translatable animal paradigm to assess probabilistic reward learning in a preclinical species.

Disclosures: **C. Glavis-Bloom:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; F. Hoffmann-La Roche Ltd. **D. Alberati:** A. Employment/Salary (full or part-time):; F. Hoffmann-La Roche Ltd. **T. Ballard:** A. Employment/Salary (full or part-time):; F. Hoffmann-La Roche Ltd. **M. Croxall:** A. Employment/Salary (full or part-time):; 3Lafayette Instrument Company. **K. Taylor:** A. Employment/Salary (full or part-time):; F. Hoffmann-La Roche Ltd. **D. Umbricht:** A. Employment/Salary (full or part-time):; F. Hoffmann-La Roche Ltd. **T.L. Wallace:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; F. Hoffmann-La Roche Ltd.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

Location: Hall A

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Program#/Poster#: 633.02/CC6

Topic: F.02. Animal Cognition and Behavior

Support: RGPIN 7665, Natural Sciences and Engineering Research Council (Canada).

Title: Sign-tracking to a lever-CS in autoshaping is due to instrumental learning

Authors: *M. NAEEM[1], N. WHITE[2];
[2]Psychology, [1]McGill Univ., Montreal, QC, Canada

Abstract: In autoshaping with rats a CS (lever insertion) is repeatedly followed by a US (food) regardless of what the rat does, a Pavlovian paradigm (Boakes, 1977, in H. Davis & H. M. B. Hurwitz (Eds.), *Operant-Pavlovian Interactions,* 67). Some rats (sign trackers) learn to press the lever, a response that is thought to be due to acquisition of a Pavlovian association (CS-US, or stimulus-outcome). However, lesions of the amygdala, a structure known to be critical for Pavlovian learning have limited effects on this form of sign-tracking (Chang, et al, 2012, *Brain Research*, 1450, 49; 2012, *Neurobiology of Learning and Memory*, 97, 441), raising questions about whether the learning underlying the lever press response is in fact Pavlovian. An alternative is based on the fact that every lever-press response made by a sign-tracker is reinforced after the end of the CS (Williams & Williams, 1969, *Journal of the Experimental Analysis of Behavior*, 12, 511), on what amounts to an interval schedule, suggesting that the response could be due to instrumental learning. To test this hypothesis rats with lesions of structures known to be critical for instrumental learning were trained in an autoshaping

paradigm. Thirty six per cent (7/19) of the rats in the sham-lesioned control group were sign-trackers (lever press before food magazine entry on most trials); no rats with lesions of either dorsolateral (DLS, n=8) or dorsomedial (DMS, n=9) striatum were sign-trackers. Rats with DMS, but not DLS, lesions increased their frequency of magazine entries. These findings are consistent with the hypothesis that sign-tracking with a lever press response is primarily due to (non-Pavlovian) instrumental learning, probably some combination of action-outcome and S-R associations. However, amygdala lesions do impair sign-tracking measured as simple approach to the CS with no additional response (e.g., Hatfield, et al, 1996, *Journal of Neuroscience*, *16*, 5256; Parkinson, et al, 2000, *European Journal of Neuroscience*, 12, 405), suggesting that behavior may be due to Pavlovian learning.

Disclosures: **M. Naeem:** None. **N. White:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 633.03/CC7

Topic: F.02. Animal Cognition and Behavior

Support: NIMH DIRP

Title: Behavioral flexibility in reversal learning of “what” vs “where”: a Bayesian approach

Authors: ***R. BARTOLO**, L. KENNERLY, V. D. COSTA, B. B. AVERBECK; NIMH/NIH, Bethesda, MD

Abstract: Learning comes in many forms and separable circuits may underlie learning stimulus-reward vs. location-reward associations. To begin to examine this hypothesis, we have trained two macaques on a stochastic, two-armed bandit oculomotor reversal learning task. In the task, animals have to learn to associate either locations or objects with rewards in randomly interleaved blocks of 80 trials. In each block one of two stimuli (circle or square - stimulus blocks, n=226) or one of two locations (left or right - location blocks, n=223) had a higher reward probability with respect to the other according to one of three possible reward schedules (0.6/0.4, 0.7/0.3, and 0.8/0.2). The block types were not cued and animals had to infer whether locations or objects were relevant in each block. For both block types, at a random trial between the 30th and 50th, reward mappings were inverted across the two targets (stimuli or locations), and the animals had to reverse their choice preference. Behavior was analyzed by fitting a Bayesian model to the data. The model was based on our previously published model (Costa et

al., 2015, J. Neurosci. 35(6):2407-2416). However, it was extended to account for the two different block types (stimulus or location learning). The model allowed us to estimate posterior distributions over block type (stimulus or location) and reversal trial. Furthermore, two versions of the model were used to estimate 1) the trial at which the animals reversed their choices (behavioral model) and 2) the trial at which an ideal observer would reverse its choices, based on the previous outcomes. The absolute value of the difference between estimates from the two models, an index of the animal's reversal sensitivity, decreased for easier schedules for both location and stimulus blocks. However, a 2-way ANOVA revealed a significant schedule×block-type interaction effect ($F_{368,2}=7.04$, $p=0.001$). To assess if switching from one block type to another had an effect on choice behavior, we analyzed choices by plotting the choice rate for the initially more rewarded target. Data were split according to the previous and current block types to assess if switching block type had an impact on the choices. After the first trial, choice-rates increased quickly for the most rewarded target, independently of the previous block's type. Bayesian estimates of block-type posterior probabilities across trials quantified this, and were affected only by the reward ratio. In summary, acquisition was similar between stimulus and location blocks, but reversal performance showed differences.

Disclosures: **R. Bartolo:** None. **L. Kennerly:** None. **V.D. Costa:** None. **B.B. Averbeck:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

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Support: Emory Neuroscience Initiative grant

NIMH R21MH97187

NIMH P50MH100023

NINDS 1T90DA032466-03

Title: Measuring and manipulating corticostriatal functional neural circuitry in the socially monogamous prairie vole

Authors: *E. A. AMADEI[1], Z. V. JOHNSON[2], J. KWON[2], A. C. SHPINER[3], V. SARAVANAN[2], W. D. MAYS[4], L. J. YOUNG[5,6,7], R. C. LIU[4,7];
[1]Georgia Tech. and Emory Univ., Atlanta, GA; [2]Neurosci. Grad. Program, [3]Neurosci. and

Behavioral Biol. Program, [4]Biol., [5]Psychiatry and Behavioral Sci., [6]Yerkes Natl. Primate Res. Ctr., [7]Ctr. for Translational Social Neurosci., Emory Univ., Atlanta, GA

Abstract: The ability to form positive social relationships is key to mental health, and yet the underlying functional neural circuitry remains poorly understood. The socially monogamous prairie vole is a canonical animal model for social bonding. Previous anatomical, genetic, and pharmacological studies have implicated two corticostriatal nodes – the medial prefrontal cortex (mPFC) and nucleus accumbens (NAcc) – in vole social bond formation. However, these approaches do not provide a dynamic view of the functional neural activity and connectivity of these regions during social interactions leading to a bond. To address this, we measured and manipulated neural activity within this circuit in socially-behaving female voles. We found an enhancement in low-frequency mPFC-to-NAcc connectivity during mating, a behavior that accelerates vole bond formation, compared to the control, non-social behavior of self-grooming. Further, optogenetically stimulating mPFC afferents to the NAcc at low frequencies in the absence of mating shifts later behavioral preference towards a partner, suggesting that low-frequency activation of this circuit is functionally relevant for bond formation. Finally, phase-amplitude coupling from mPFC to NAcc is enhanced during mating, suggesting that mPFC activation during social bonding drives NAcc by rhythmically modulating its excitability. Together, these results reveal a dynamic picture of corticostriatal activation during bond formation, with exciting implications for how affiliative social interactions can recruit reward and reinforcement systems to drive changes in behavior. A key ongoing direction is to determine the role of neurochemicals (e.g. oxytocin) in modulating this system.

Disclosures: **E.A. Amadei:** None. **Z.V. Johnson:** None. **J. Kwon:** None. **A.C. Shpiner:** None. **V. Saravanan:** None. **W.D. Mays:** None. **L.J. Young:** None. **R.C. Liu:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

Location: Hall A

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Program#/Poster#: 633.05/CC9

Topic: F.02. Animal Cognition and Behavior

Title: Post-extinction inactivation of the dorsolateral striatum blocks extinction of egocentric response learning, but not place learning, in the plus-maze

Authors: *J. GOODMAN, M. G. PACKARD;
Inst. for Neurosci., Texas A&M Univ., College Station, TX

Abstract: In the response learning version of the plus-maze task, animals acquire an egocentric turning response that may serve as an exemplar of the stimulus-response/habit memory system. Whereas extensive research has investigated the neural substrates supporting initial acquisition, little research has examined the neural substrates supporting extinction of response learning. The present study examines whether the dorsolateral striatum (DLS), which is critical for initial acquisition, might also be required for extinction of response learning. In addition the present study examines whether the role of the DLS in extinction is selective to response learning or whether it might also be implicated in extinction of place learning. In the response learning task, adult male Long-Evans rats were released from varying start points (North, South) and were reinforced to make the same egocentric turning response (e.g. turn left) at the choice point to receive a palatable food reward at the end of a separate goal arm (East or West). In the place learning task, animals were released from varying start points and were reinforced to go to a consistent goal arm (e.g. the West arm) to receive the food reward. Following initial acquisition in both tasks, animals were given two days of extinction training, which was conducted in a manner identical to initial acquisition except without the food reward. Immediately after the first day of extinction, animals received bilateral intra-DLS infusions of bupivacaine (0.75%) or physiological saline, and effects of drug were examined on the second extinction day. In the response learning task, post-training administration of bupivacaine blocked consolidation of extinction, whereas in the place learning task bupivacaine was ineffective. These results suggest that the DLS is selectively required for the consolidation of extinction in a DLS-dependent response learning task, but not in a place learning task. In view of evidence that the DLS-dependent habit memory system may underlie some symptoms of human psychopathologies (e.g. drug addiction), the present findings may be useful in determining the neurobiological mechanisms that support the suppression of habit-like symptoms in these disorders.

Disclosures: J. Goodman: None. **M.G. Packard:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

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Program#/Poster#: 633.06/CC10

Topic: F.02. Animal Cognition and Behavior

Support: IWT (the government agency for Innovation by Science and Technology)

Title: The contribution of dorsomedial and dorsolateral striatum during different phases of Morris water maze training

Authors: *T. POOTERS[1], I. GANTOIS[2,1], B. VERMAERCKE[1], R. D'HOOGE[1];
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Abstract: Impairments in cognitive and executive functioning occur in different basal ganglia disorders (e.g. schizophrenia and Parkinson's disease), and remain largely intractable with available treatments. The striatum, the largest area of the basal ganglia, has been suggested to contribute significantly to these cognitive deficits, but the specific role and time-dependent involvement of striatal subregions in cognitive (dys)functioning remain unclear. Therefore, we studied spatial learning and memory in mice with lesions in dorsomedial (DMS) and dorsolateral striatum (DLS). Animals were trained for 15 days in the hidden-platform version of the Morris water maze. To determine the time-dependent involvement of DMS and DLS, lesions were applied during different phases of MWM training (before training or after 5 or 10 days of acquisition training). Compared to sham controls, animals that received DMS damage before training were severely impaired during acquisition training, whereas animals with DLS lesions did not show any impairment at all. DMS-damaged mice displayed delayed acquisition, increased thigmotaxis and increased distance to the platform during the entire course of training, but when lesions were applied after 5 or 10 days of training, performance was similar to controls. Search strategy analysis indicated that the deficits due to DMS damage coincided with decreased ability to switch flexibly between spatial, non-spatial and repetitive search strategies. In conclusion, these data suggest that DMS (but not DLS) is crucial during the initial phase of acquisition, and that DMS controls goal-directed behaviours.

Disclosures: T. Pooters: None. **I. Gantois:** None. **B. Vermaercke:** None. **R. D'Hooge:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: F.02. Animal Cognition and Behavior

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NSF Grant DMS-1042134

Title: Context-dependent action selection mediated by specific temporal coordination between prefrontal cortex and striatum

Authors: *S. ARDID, J. SHERFEY, M. M. MCCARTHY, N. KOPELL;
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Abstract: In rule-based decision tasks, the proper response to a stimulus varies depending on context or "rule". The behavioral performance may also differ; for instance in response to color vs. orientation of a bar, responses are faster for orientation. Rule selective neurons have been identified in prefrontal cortex (PFC). However, the underlying dynamics are not fully understood. Recently, Buschman et al. have shown that the activity of rule selective cells is temporally coordinated. Around stimulus onset, high β rhythmic activity emerges in the frontal cortex simultaneously in neurons encoding alternative rules (color and orientation). However, (1) the magnitude of this synchrony is higher for the neurons encoding the active rule, and (2) the increase in synchrony is significantly larger when the dominant rule is active (orientation trials), compared to when the subordinate rule is active (color trials). Rhythmic activity at α frequencies, on the other hand, appears before stimulation, but specifically under the subordinate condition (color trials), and only for those PFC neurons encoding the dominant dimension (orientation selective cells). These observations suggest specific functional roles for the two types of rhythmic activity. First, high β rhythmic inputs may stimulate downstream striatal neurons to activate the associated motor response. Second, α rhythm inputs to downstream striatal neurons may trigger inhibitory control of salient information that is behaviorally irrelevant. Here we show in a modeling framework that the rhythmic activity in PFC may activate alternative pathways of the basal ganglia, mechanistically via local interactions with distinct intrinsic resonances within the striatal circuit. We have built a model of the striatum composed of D1 and D2 receptor medium spiny neurons (D1 and D2 MSNs), which represent the input stage of the direct and indirect pathways of the basal ganglia, respectively. PFC inputs in the model do not show any bias with respect to D1 vs. D2 MSNs. The frequency at which D1 and D2 MSNs cells resonate depends on the excitability of each cell type in the circuit, so the higher the excitability, the higher the frequency at which the cells oscillate in the model. Our model is based on a regime of higher excitability for D1 MSNs compared to D2 MSNs. Results from the model demonstrate that when D2 MSNs resonate at β1 (low β) frequencies and D1 MSNs resonate at β2 (high β) frequencies, a rhythmic input from PFC at either α vs. high β frequencies is capable of enforcing a β1 vs. β2 rhythm in the local circuit. Hence, inputs from PFC at different frequencies are capable of activating respectively the indirect vs. direct pathway of the basal ganglia.

Disclosures: S. Ardid: None. **J. Sherfey:** None. **M.M. McCarthy:** None. **N. Kopell:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

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ARO W911NF-12-R-0012-02

Title: Modeling neuronal diversity and fast network oscillations in rat anterior cingulate cortex (ACC)

Authors: *J. S. SHERFEY[1], N. E. ADAMS[2,3], F. E. N. LEBEAU[3], N. KOPELL[1,2];
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Abstract: Fast network oscillations (gamma: 30-80Hz, beta: 15-30Hz) and flexible population activity are thought to underlie many of the cognitive functions associated with the ACC. We recently demonstrated that activation of the glutamatergic system evokes robust beta and/or gamma-frequency network oscillations in rat ACC (analogous to primate ACC/PFC) *in vitro* and that ACC neurons exhibit a wide diversity of response properties. We used cluster analysis to further investigate the organization of ACC cell diversity and then computational modeling to study its mechanistic origins and relation to fast network oscillations. First, the intracellular recordings from ACC neurons were analyzed to extract 10 intrinsic response properties (IPs) for each neuron. Cluster analysis grouped the ACC neurons into 5 classes with 4 IPs explaining >80% of the variance: after-hyperpolarization duration, spike width, spike rate at threshold, and resting membrane potential. However, neuron classes were broad and partially overlapping, suggesting they may represent physiological regimes between which ACC neurons could transition depending on their biophysical state. The mechanistic basis of ACC cell diversity was explored using conductance-based models with 10 ion currents known to exist in ACC/PFC. A set of models capturing the observed diversity was obtained by varying maximal conductances and fitting IPs to the 5 most explanatory distributions. Across the resulting cell models, each intrinsic property was regulated by a distinct set of currents suggesting how coordinated changes in potassium, sodium, and calcium channels could switch a given cell from one class to another. Next, the heterogeneous model population was coupled to inhibitory interneurons with time constants of inhibition based on IPSPs observed experimentally in cells rhythmic with the network beta or gamma-frequency oscillation. The resulting ACC network model replicated the different frequencies observed experimentally and demonstrated that cell diversity spreads out network frequencies without disrupting the underlying oscillation. These results suggest distinct interneuron populations in ACC pace beta and gamma-frequency network oscillations capable of temporally grouping diverse cell activities into flexible assemblies for task-relevant processing.

Disclosures: **J.S. Sherfey:** None. **N.E. Adams:** None. **F.E.N. LeBeau:** None. **N. Kopell:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

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Title: Balancing consistency with flexibility in anterior cingulate cortex (ACC) action representations

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Abstract: Efficient, flexible behavior involves detecting the differences as well as similarities in the actions required to deal with new situations. The anterior cingulate cortex (ACC) has been implicated in action planning or action monitoring/control and while it does not directly generate actions, it may alter the way they are represented across different situations. The present study quantified the flexibility of ACC action representations by recording from neurons as rats performed 3 different operant actions (a nose-poke, lever press and wheel turn) in two different sequences or contexts. Consistent with past studies, ACC ensembles exhibited unique activity state patterns during the performance of each action and the action-specific patterns were shifted by a switch in the context or sequence. Importantly, the magnitude of the context or sequence dependent shift was well equalized across the 3 actions and as a result the separation between the 3 action representations was the same before and after the switch. The equalized movement was a result of highly balanced increases versus decreases in firing across the population. When neurons were sorted according to their selectivity for actions (versus the baseline period), a well-defined selectivity curve was observed. Remarkably the same selectivity curve appeared after the sequence or context switch but the sorting order was now completely different. This indicated a high degree of remapping and accordingly only the top 10% most action selective neurons maintained the same degree of selectivity before/after the switch. Using leave-one-out variant of

Support-Vector-Machine (SVM) decoding, we found that individual neurons varied in their selectivity for the 3 actions on a trial by trial basis. PCA was then run on the SVM scores of all neurons but separately for each action. PC1 and PC2 were virtually identical across the 3 actions: PC1 always exhibited stable values before/after the switch and likely reflected the consistent encoding of the actual actions themselves. PC2 attained high values in sequence 1 but dropped precipitously at the sequence 1 to 2 transition point and this drop was synchronous across the 3 actions. The similarity of PC1 and PC2 across the 3 actions was only present at the ensemble level as single neurons could exhibit a PC1- or PC2-like pattern on any combination of the 3 actions. Collectively these results suggest that individual ACC neurons track subtle differences in actions across different situations but by balancing all these changes across the population, ensemble representations maintain a high degree of consistency.

Disclosures: **J.K. Seamans:** None. **L. Ma:** None. **D. Durstewitz:** None. **J. Hyman:** None.

Poster

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Support: CIHR

CONACYT

Title: Coding of emotional valence in the rodent Anterior Cingulate Cortex (ACC)

Authors: *B. CARACHEO[1], J. GREWAL[2], J. SEAMANS[3];
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Abstract: The vast majority of basic research on the Anterior Cingulate Cortex (ACC) has focused on it role in cognition. Yet the ACC is classically 'emotional' cortex and the results from human imaging experiments as well as lesions (anterior cingulotomies) indicate that the coding of emotional valence may be an equally or even more important function. Here we investigated how ACC neurons in rats represent periods of varying emotional valence. The task was simple and straightforward. The first stage consisted of 3 blocks and in each block a unique auditory tone (conditioned stimulus, CS) was paired with one of 3 unconditioned stimuli (US), a shock (negative valance US), the delivery of food (positive valance US) or nothing (neutral US). Each

CS was presented for 5 seconds before the US, and the pair was presented at 20-60 second intervals. In the second stage of the task, the CS-US pairs were interleaved within one task block. Sixteen tetrodes implanted in the ACC recorded neural activity over at least four sessions from four rats. Neural activity was recorded and characterized using single unit activity selectivity indices, principal component analysis (PCA), probabilistic states through Hidden Markov Models (HMM) and measures of entropy and complexity. At the ensemble level, HMM and PCA identified unique neural states that emerged during the presentation of each CS-US pair, as well a baseline state. Analyses of single unit selectivity revealed neurons that responded to the CSs, the USs, or some combination of both. Single neurons could also respond to various combinations of 2 CSs but none were found that responded to all 3. Surprisingly, using these traditional measures we have yet to find clear evidence that the neutral CS was encoded any differently from the valanced CSs. These results are therefore consistent with the conclusions of our studies of ACC activity during cognitive tasks. Namely that ACC neurons represent whatever the animal is currently experiencing or doing. We are now considering different coding schemes that could represent 'emotional states' as distinct from discrete events.

Disclosures: **B. Caracheo:** None. **J. Grewal:** None. **J. Seamans:** None.

Poster

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Support: NSERC

Title: Unilateral naris occlusion effectively abolishes gamma oscillations in the rat ventral striatum

Authors: ***J. E. CARMICHAEL**[1,2], J. M. GMAZ[2], M. A. A. VAN DER MEER[1,2];
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Abstract: The ventral striatum (vStr), an anatomically heterogeneous region, receives a convergence of anatomical connections from structures in the cortico-striatal-thalamic loop, as well as from the hippocampal formation and amygdala. Prominent gamma-band oscillations can be recorded from the vStr local field potential (LFP), to which fast-spiking interneurons in particular can show strong phase locking. Furthermore, vStr gamma oscillations can cohere with

anatomically related areas, raising the possibility that these oscillations may reflect a dynamic routing mechanism. However, what combination of underlying sources is responsible for generating gamma oscillations recorded in the vStr remains unknown. In Experiment 1, we used high-density silicon probes with regular site spacing to reveal the phase and amplitude distributions of LFP oscillations across a region of the vStr (1.4mm2). Rats (n = 4) were recorded while they rested on a pedestal or engaged in a foraging task. Neither condition yielded evidence of sources or sinks in the power of the gamma oscillations across the vStr, for either low-gamma, high-gamma, or indeed any other frequency band. Instead, we found a consistent linear gradient of gamma power which increased in the ventrolateral direction, suggested that the source of these gamma oscillations may lie outside of the vStr. The adjacent piriform cortex has been suggested as a possible source of gamma oscillations in vStr (Berke, 2009). To test this possibility directly, Experiment 2 used a reversible unilateral naris occlusion procedure, known to abolish piriform gamma oscillations ipsilateral to the occlusion (Zibrowski & Vanderwolf, 1997). In rats (n = 3) with unilateral electrodes implanted into the vStr, gamma power was effectively abolished during ipsilateral naris closure, while contralateral occlusion and controls showed no effect on gamma power. This suggests that the gamma signal reported in previous literature is likely not locally generated within the vStr. Taken together, these results demonstrate that although strong gamma oscillations can be found in the vStr LFP, these oscillations are in fact volume-conducted from the piriform cortex. Phase-locking to this rhythm within the vStr may be the result of inputs from piriform cortex pyramidal cells onto vStr neurons. This updated view of vStr oscillations has important implications for studies of “functional” or “effective” connectivity involving the vStr and associated regions. Strong coherence between vStr and its in- and outputs may be due to common input from piriform cortex, rather than a local or pairwise implementation of a gain modulation or routing mechanism.

Disclosures: **J.E. Carmichael:** None. **J.M. Gmaz:** None. **M.A.A. van der Meer:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

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Topic: F.02. Animal Cognition and Behavior

Title: Environmental enrichment and striatal perineuronal net dissolution exert opposing behavioural effects in the puzzle-box task

Authors: *A. M. O'CONNOR, C. A. LEAMEY, A. SAWATARI;
Bosch Inst., University of Sydney, Australia

Abstract: Environmental enrichment (EE) provides animals with increased sensory, motor and social stimuli. Previous work has demonstrated that EE from birth can improve performance in cognitive behavioural tasks and accelerate the maturation of Perineuronal nets (PNNs) within the striatum, an important component of basal ganglia circuitry. Although both EE and the enzymatic removal of PNNs can adjust levels of plasticity in established neural circuits, the manner in which these processes remain related is unclear. As a first step, we examined the impact and interaction of both EE and striatal PNN removal upon behaviours of animals within the Puzzle-Box task, a test of goal-orientated learning and problem solving. C57BL6J mice were raised within standard (S) and enriched (E) housing conditions until 12 weeks old. Performance of untreated animals (S, n=18; E, n=21), mice receiving striatal Chondroitinase ABC (ChABC) injection (SC, n=8; EC, n=13), and animals receiving striatal vehicle injection (SV, n=7; EV, n=13) within the Puzzle-Box was assessed by the time taken to solve obstruction puzzles. Video recordings were taken and assessed using TopScan software, with the Puzzle-Box arena divided into various zones to analyse behavioural patterns. There was a significant effect of treatment group upon time taken to solve the Puzzle-Box ($P<0.001$), with E animals taking less time and SC animals taking more time than other treatment groups. E animals travelled less distance than all other treatment groups ($P=0.001$), spent a lesser proportion of time directly next to the walls of the arena ($P=0.012$) and a greater proportion of time engaged with obstruction puzzles ($P=0.001$). SC animals spent a greater proportion of time directly next to the walls of the arena than S mice ($P=0.033$). EE animals exhibited shorter latencies to solve puzzles within the apparatus, as well as decreased locomotor hyperactivity, altered thigmotactic behavioural patterns, and increased engagement with novel obstruction puzzle objects. Striatal ChABC treatment had an opposite effect in both standard and enriched animals, increasing the time taken to solve Puzzle-Box tasks, increasing thigmotactic behavioural patterns, and decreasing interaction with novel obstruction puzzle objects. Our results demonstrate that EE and striatal PNN dissolution exert opposing behavioural effects, suggesting that there may be levels of plasticity within the striatum worked upon by these treatments.

Disclosures: **A.M. O'Connor:** None. **C.A. Leamey:** None. **A. Sawatari:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

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Topic: F.02. Animal Cognition and Behavior

Support: NSERC

Title: Incidental learning in the ventral striatum elicits context-specific inhibition in a visual discrimination task supported by the dorsolateral striatum

Authors: *D. C. GIDYK, C. M. BYE, K. M. NIEDERMEIER, R. J. MCDONALD; Neurosci., Univ. of Lethbridge, Lethbridge, AB, Canada

Abstract: Multiple memory systems theory states that in the mammalian brain, mnemonic function is organized into multiple neural systems. These systems are complex, operate in parallel, and support different forms of learning and memory through dynamic cooperative and competitive interactions. Our previous work has provided empirical support for multiple memory systems theory through the dissociation of learning and memory function in the rat during different behavioural tasks. In cases where one neural system is necessary for learning and memory on a given behavioural task, other systems may acquire incidental information that can be uncovered under certain testing conditions. A demonstration of this can be seen in a series of studies in our lab that discovered that an incidentally acquired context-specific inhibitory representation is acquired by the ventral hippocampus (vHPC) during a striatal-dependent stimulus-response (S-R) visual discrimination task. We hypothesize that the ventral striatum (VS) is a key part of the circuit mediating context-specific inhibition due to it's connectivity with the vHPC and medial prefrontal cortex (mPFC). It is our view that the VS is part of a system that suppresses or invigorates actions for goal-directed and habitual behaviours which are dependent on the dorsomedial striatum (DMS) and dorsolateral striatum (DLS) respectively. The present study was designed to asses the hypothesis that the VS is a key part of the circuit mediating the context-specific inhibition effect described in our previous work. Sixteen male Long-Evans rats were trained on an S-R visual discrimination task (8-arm radial arm maze; RAM) in either context A or context B under a reward contingency of either lit arms or dark arms predicting the presence of a food reward (L+ D- and L- D+ respectively) in a counterbalanced manner. After reaching a set performance criterion, rats were then trained in the new context with the reward contingency reversed and again trained to criterion. All rats received chronic bilateral cannula implants into the VS allowed to recover, then given a single competition test after Ropivacaine or Saline infusion into VS. The results of this study will contribute to the understanding of multiple memory systems and which neural substrates are critical for the formation and expression of context-specific inhibition.

Disclosures: D.C. Gidyk: None. **C.M. Bye:** None. **K.M. Niedermeier:** None. **R.J. McDonald:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

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Title: Role of the dorsolateral and dorsomedial striatum in reward learning

Authors: *A. LIPKIN, H. BERGSTROM, C. PICKENS, C. PINARD, A. HOLMES;
Lab. of Behavioral and Genomic Neurosci., Natl. Inst. On Alcohol Abuse and Alcoholism, Rockville, MD

Abstract: Brain processes of reward learning are essential for shaping and guiding decision-making. Dysfunctions of reward learning can lead to maladaptive behaviors such as addiction. The dorsal striatum is required for mediating various forms of reward learning. The dorsal striatum is functionally subdivided into lateral (DLS) and medial (DMS) zones, based on differences in patterns of cortical innervation and contributions to various forms of reward learning. However, the exact contribution of the DLS and DMS to reward learning, and the specific components of reward learning these regions mediate are not understood. To test reward learning, we used an operant task in which mice must first visually discriminate objects presented on a touchscreen display and then physically touch the one that predicts an appetitive reward. Prior to visual discrimination learning, an adeno-associated viral construct (rAAV8/CAG-ArchT-GFP) was bilaterally expressed in a population of DLS neurons in C57BL/6J mice. Silencing DLS neurons when mice made a “choice” on the touchscreen facilitated discrimination learning, as compared to controls expressing an inactive virus (rAAV8/CAG-GFP). Facilitated learning was accompanied by reduced errors rates, shorter strings of incorrect responses, and increased win-stay and lost-shift probabilities in the earliest stages of learning. By contrast, silencing DLS neurons during reward collection did not affect performance. To dissect the relative contribution of the DLS-Direct and Indirect pathways in reward learning we used D1-Cre and A2A-Cre mutant mice, respectively. We found that silencing the D1-direct pathway (rAAV5/EF1a-DIO-eArch3.0-eYFP) largely recapitulated the results of DLS-ArchT-CAG inhibition, with a greater percentage of correct responses, shorter strings of incorrect responses, and increased win-stay and lose-shift probability in the earliest stages of learning. Silencing the (A2) “indirect” pathway resulted in a reduction in errors at the early stages, but no change in correct responses. In contrast to DLS inhibition, silencing DMS neurons attenuated discrimination learning, increased total errors and decreased win-stay probabilities. Overall, these results support a model whereby the DLS and DMS compete for

control over performance over reward learning. Further, these results provide support for the view that the direct and indirect pathways work do not necessarily work in opposition in the acquisition of reward learning. This series of experiments provide new insight into how the DLS direct and indirect pathways functionally contribute to visual discrimination learning.

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Poster

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Title: Optogenetic stimulation of striatum during an active visual change detection task in mice

Authors: *L. WANG, K. RANGARAJAN, R. J. KRAUZLIS;
NIH, Natl. Eye Inst., Bethesda, MD

Abstract: The role of the striatum in associating relevant sensory information with rewarded motor actions is well established. The striatum is also implicated in sensory discrimination, but because most studies measure behavior with orienting movements, it can be difficult to dissociate motor bias from sensory discrimination *per se*. To address this issue, we trained mice to report changes in the orientation of drifting gratings by licking or not licking a central spout (yes/no task), and used transgenic mice to optogenetically stimulate specific types of neurons in the striatum. Mice were head-fixed and ran on a styrofoam wheel within a sound-attenuating chamber during presentation of the visual stimuli, displayed on two flat panels. The visual stimuli consisted of two (left and right) vertically oriented Gabor patches superimposed on a pink noise background. Mice initiated each trial by running or walking, and the distance traveled on the wheel controlled the visual stimuli. During individual trials, the drift speed of the two vertical gratings was determined by the running speed of the mice, and after a randomized distance was traversed, one of the two gratings changed its orientation. The task of the mice was to lick the spout if an orientation change happened on either side of the display, and to withhold from licking before the change occurred. Correct responses were rewarded by a drop of soymilk, and premature licks prompted auditory feedback and a timeout penalty. We used *Drd1a-Cre* and *A2a-Cre* mice to target the direct and indirect pathway medium spiny neurons (MSNs) in the

striatum. Cre-dependent virus AAV2-DIO-ChR2 was unilaterally injected into the dorsal striatum of these mice. During optogenetic stimulation experiments, brief low intensity (0.05-0.2mW) 465nm continuous light was delivered to the striatum through an implanted optic fiber at the onset of the orientation change in a randomized subset of trials. Our preliminary data show that: 1) with optogenetic stimulation in both Drd1a and A2a-Cre mice, there was a significant increase of hit rate when the orientation change occurred contralateral to the stimulation side, but not when the visual changes was on the ipsilateral side; 2) there was a reduction of mouse running speed during the stimulation epoch compared to no-stimulation controls. These results show that MSNs in both the direct and indirect pathways in the striatum contribute to the performance of the visual change detection task. Our preliminary finding that the effects were selective for visual changes on the contralateral side suggests that the optogenetic stimulation affected sensory discrimination *per se* rather than simply introducing a motor bias.

Disclosures: **L. Wang:** None. **K. Rangarajan:** None. **R.J. Krauzlis:** None.

Poster

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Title: Representation of learned action sequences in the dorsolateral corticostriatal circuit

Authors: *N. MARTIROS[1,2], A. M. GRAYBIEL[1,2];
[1]Brain and Cognitive Sci., [2]McGovern Inst. for Brain Res., MIT, Cambridge, MA

Abstract: Well-ingrained behaviors often consist of a series of actions “chunked” together and executed in an automated manner. The dorsolateral striatal circuit is known to be important for the execution of such behaviors, but how neural activity in this region subserves this functional role is not understood. To test how neurons in this region of striatum represent such learned

action sequences, we designed a self-paced task in which each rat learned to perform a unique sequence of three lever presses in order to obtain a reward. After performing a clustering procedure on the task response profiles of single neurons, we found that the phasic responses of the striatal projection neurons recorded from rats that learned six possible 3-step lever press sequences occurred at four distinct trial periods: around the time of the first lever press, the time of the last lever press, at reward delivery, and during an extended period during reward consumption. Together with previous finding in our laboratory that a similar pattern of responses occurs during the performance of a T-maze task, we conclude that in a variety of reinforced behaviors requiring movements of different nature and timing, projection neurons in the dorsolateral striatum universally represent the initiation/termination or transitions between behaviors rather than having only simple motor responses. To explore how these patterns of activity are influenced by the corticostriatal link in this circuit, we recorded simultaneously from the region of motor cortex with dense projections to the targeted striatal region. Contrasts between the activity in the motor cortex and dorsolateral striatum were notable, including with respect to the occurrence of the beginning-and-end accentuation patterns. Whereas the beginning-and-end patterning was conspicuous in many striatal neurons, it was less evident in the motor cortical populations recorded. Ongoing optogenetic experiments exploring this corticostriatal circuit are addressing the role of the motor cortical input in the task-related neuronal firing of striatal projection neurons.

Disclosures: **N. Martiros:** None. **A.M. Graybiel:** None.

Poster

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Topic: F.02. Animal Cognition and Behavior

Title: Devascularization of sensorimotor cortex produces persistent deficits in a string pulling task

Authors: ***A. BLACKWELL**[1], W. L. WIDDICK[1], J. L. CHEATWOOD[2], D. G. WALLACE[1]; [1]Northern Illinois Univ., Dekalb, IL; [2]Southern Illinois Univ., DeKalb, IL

Abstract: Previous work investigating fine motor control and unilateral sensorimotor cortex lesions typically utilized behavioral assessments that require extensive training. The spontaneous string pulling behavior observed in rats may provide a novel technique to characterize the fine motor control deficits associated with rodent models of neurological disorders. The current study

assessed the ability of movement organization observed during string pulling behavior to dissociate persistent motor deficits from compensatory mechanisms associated with permanent sensorimotor cortex devascularization. Twelve male Long-Evans rats were given eight trials a day for three days to retrieve a cashew by pulling a string of increasing length. Subsequent to training, rats received either sensorimotor devascularization (n=7) or sham (n=5) surgeries and string pulling behavior was assessed one day, three days, and once per week to 70 days. Following behavioral testing, brains were extracted, sliced in coronal sections, and stained with Cresyl Violet for histological analyses of lesion extent. Initially rats with sensorimotor devascularization took longer to retrieve the cashew relative to sham rats; however this deficit abated across testing days. In contrast, a persistent difference was observed in the number of misses observed between rats with sensorimotor devascularization and sham surgery rats. This persistent deficit was most pronounced in the contra-lesion forelimb. These results demonstrate the potential of string pulling behavior as a robust assessment of fine motor control that involves bimanual coordination and depends on relatively few training trials.

Disclosures: A. Blackwell: None. **W.L. Widdick:** None. **J.L. Cheatwood:** None. **D.G. Wallace:** None.

Poster

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Topic: F.02. Animal Cognition and Behavior

Title: Neglecting to protect: Unilateral DCS lesions disrupt food protection behavior organization

Authors: *P. A. BLANKENSHIP[1], C. N. WOLF[1], J. L. CHEATWOOD[2], D. G. WALLACE[1]; [1]Psychology, Northern Illinois Univ., Dekalb, IL; [2]Anat., Southern Illinois Univ., Carbondale, IL

Abstract: Multimodal neglect is a spatial impairment characterized by an inability to detect stimuli or direct movement to one side of the body. The dorsocentral striatum (DCS) has been shown to be an important component of a corticostriatal network responsible for egocentric processing. The current study evaluated the role of the DCS in food protection behavior. Both egocentric and temporal information processing have been shown to contribute to the organization of food protection behavior. Egocentric processing has been shown to influence the ability to detect an incoming conspecific and successfully protect a food item. Temporal processing has been shown to influence the transition between dodging (large lateral movements)

and bracing (pivoting about the hind limbs). Female Long-Evans rats received unilateral infusions of NMDA or saline into the DCS and subsequently served as dodgers tasked with protecting a food item from a robber conspecific. Analysis of food protection behaviors yielded significant group differences. DCS lesion animals accrued more thefts than sham operated animals. Examining this effect revealed that thefts were lateralized to the side contralateral to the lesion. Additionally, significant group differences were observed in the transition between food protection behaviors. DCS animals transitioned from dodges to braces much later than sham operated animals. Observed disruption of food protection behavior in DCS animals is consistent with deficits in egocentric and temporal processing. This work demonstrates the potential of using organized spontaneous behavior to investigate an animal model of neurological disorders such as multimodal neglect.

Disclosures: P.A. Blankenship: None. **C.N. Wolf:** None. **J.L. Cheatwood:** None. **D.G. Wallace:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 633.19/CC23

Topic: F.02. Animal Cognition and Behavior

Support: Klarman Family Foundation

NSF 1456560

Title: Frontal cortical circuits for the control of consummatory behavior

Authors: *L. M. AMARANTE[1], M. S. CAETANO[2], M. M. CLASEN[1], K. SWANSON[1], B. WETZELL[1], M. LAUBACH[1];
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Abstract: The medial prefrontal cortex (mPFC) is a crucial structure for processing reward values and exerting control over action. Neuronal ensembles in the mPFC exhibit changes in activity when animals initiate consummatory behavior (Horst and Laubach, 2013). These changes in firing rates are accompanied by phase-locking in cortical theta rhythms (Horst and Laubach, 2013). These neural signals are concentrated in the rostral part of the prelimbic cortex, an area that may be homologous to the ventromedial/orbitomedial frontal cortex in primates. Reversible inactivations of this region eliminate the expression of incentive contrast for liquid

sucrose rewards and temporally fragment licking (Parent et al., 2015). In the present study, we examined functional circuits linking the rostral mPFC with subcortical brain regions associated with homeostatic and reward related processing. In addition, we compared functional connections between the rostral mPFC and the laterally adjacent agranular cortex, which contains the putative oral motor cortex in rodents. Electrical and optogenetic stimulation methods were combined with immediate early gene (IEG) mapping (c-Fos and Npas4) and anatomical tract-tracing. Stimulation of both cortical areas led to an immediate cessation of ongoing licking in rats tested in a sucrose consumption procedure. Similar results were obtained in rats tested in a delayed response task. Stimulation of both cortical areas revealed IEG expression in agranular insular cortex, paraventricular thalamic nucleus, globus pallidus, lateral hypothalamus, and medial septum. IEG expression in dorsal striatum was also evident following stimulation of the oral motor cortex, but not the rostral mPFC. These findings suggest that a common set of brain regions associated with homeostatic and reward processing are linked to frontal areas that control consummatory behavior.

Disclosures: L.M. Amarante: None. **M.S. Caetano:** None. **M.M. Clasen:** None. **K. Swanson:** None. **B. Wetzell:** None. **M. Laubach:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

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Program#/Poster#: 633.20/CC24

Topic: F.02. Animal Cognition and Behavior

Support: Alberta Innovates Health Solutions

NSERC Discovery grant

NSERC CREATE BIP U of L

Title: Modulation of cellular activity by effort and reward in Anterior Cingulate Cortex

Authors: *S. HASHEMNIAYETORSHIZI[1], K. D. SESSFORD[2], A. J. GRUBER[1], D. R. EUSTON[1];
[1]Neuroscience, CCBN, Univ. of Lethbridge, Lethbridge, AB, Canada; [2]Med., Univ. of Calgary, Calgary, AB, Canada

Abstract: Lesions in anterior cingulate cortex (ACC) of rats have been shown to induce deficits in decisions about whether to exert a certain amount of effort to achieve a reward (Walton et al.,

2002 JNS 22(24):10996-11003). However, exactly how the ACC contributes to such decisions remains unclear. To address this question, this study investigated how neurons in the ACC of rats encode costs and benefits in effort-reward decisions. We trained four rats individually on a maze which involved a choice between two effort-reward combinations. Effort was indexed by the height of a wire-mesh ramp which the rat had to climb to achieve reward. Reward consisted of varying amounts of high-calorie liquid. Both ramp height and reward amount were varied dynamically during each experimental session in a partial factorial design with three levels of effort and two levels of reward on both left and right arms of the maze. Electrophysiological recordings of spike rates were acquired from a population of cells in ACC via an array of implanted four-channel electrodes ("tetrodes"). Analysis of the recorded data demonstrated that a significant fraction of ACC cells were discriminative for effort, reward and the chosen path (left/right). As has been reported by others, the discriminative activity for reward and effort was strongest just before the climb and weak during the period before paths diverged. Of the cells selective for reward, many exhibited ramping activity leading up to the reward. Roughly one third of the recorded cells show activity discriminative of ramp height in the period immediately before climbing, while one fourth of cells encoded ramp height when climbing down the ramp after receiving reward (which, based on our observations seemed to be effortful). Hence, the ACC encodes both the anticipation of effort as well as effort as it is being exerted. The results show that the ACC has access to both the costs and benefits of a decision and therefore could guide decisions by weighing these two factors and sending the appropriate outputs to motor-related regions.

Disclosures: S. Hashemniayetorshizi: None. **K.D. Sessford:** None. **A.J. Gruber:** None. **D.R. Euston:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

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Topic: F.02. Animal Cognition and Behavior

Support: NIH T32 Postdoctoral Training Grant

JSPS Postdoctoral Fellowships for Research Abroad

Title: Neuronal signals related to self-agency in forontopolar cortex

Authors: *K. TODA[1], B. N. AFRICK[2], G. K. ADAMS[3], J.-F. GARIEPY[2], M. L. PLATT[2]; [1]Neurobio., [2]Dept. of Neurobio., Duke Univ., Durham, NC; [3]Ctr. for Translational Social Neurosci., Yerkes Primate Res. Center, Emory Univ., Atlanta, GA

Abstract: Self-agency is defined as the sense of oneself as the cause of one's own actions. This cognitive function allows oneself to feel distinct from others, and contributes to the subjective phenomenon of consciousness (Gallagher, 2000). Despite the importance of this faculty, the neural mechanisms mediating self-agency remain poorly understood. We previously reported findings from a novel self-agency task appropriate for neurophysiological studies in primates (Toda et al., 2014, SfN abstract). Here we report that neuronal activity in frontopolar cortex, an area greatly expanded during primate evolution and long-associated with the sense of self, carries signals related to self-agency in monkeys performing this task. First, we demonstrate that rhesus monkeys show evidence of self-agency in a two-stage joystick-movement task. Each trial consisted of a manipulation stage and a subsequent decision stage. In the manipulation stage, two dots and a target were presented on the display. Movement of one dot was correlated with the monkey's manipulation of a joystick (avatar), while the movement of the other dot (decoy) replayed the manipulation from the previous trial. Monkeys were required to move the avatar to the target. In the subsequent decision stage, monkeys were required to choose the color of the target they operated in the manipulation stage by moving a dot to one of two targets. To uncover the sense of agency, we compared internal and external cue conditions. In the internal cue condition, monkeys were required to detect the avatar by comparing proprioceptive and efference copy information about their movements with visual feedback. In the external cue condition, dot color directly indicated the appropriate avatar for the monkey to select. Monkeys successfully performed the manipulation stage and reported the color of the avatar during the decision stage, indicating they have a sense of their own agency and can report this information to an observer. These findings demonstrate the utility of our task for direct investigation of the neural basis of self-agency. We next asked whether and how the neurons in frontopolar cortex signal information during performance of our self-agency task. Many neurons showed task-related activity closely synched to task events. Further, some neurons appeared to signal agency-detection and/or agency-based decisions. Nevertheless, differential activity in the internal and external cue condition was rare. We also observed robust feedback-related activity in this area. Future studies of the impact of pharmacological inactivation of this area may reveal the functional contributions of these signals to the sense of agency.

Disclosures: K. Toda: None. **B.N. Africk:** None. **G.K. Adams:** None. **J. Gariepy:** None. **M.L. Platt:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

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Topic: F.02. Animal Cognition and Behavior

Support: 1P50MH086400-05

NIH-NEI - 2R01EY017658-06A1

Title: Neural dynamics between the basal forebrain and the dorsolateral prefrontal cortex during wakefulness, sleep and anesthesia

Authors: *Y. ISHIZAWA[1], C. MARTINEZ-RUBIO[2], A. PAULK[2], J.-B. EICHENLAUB[3], S. S. CASH[3], E. ESKANDAR[2];
[1]Anesthesia, Critical Care & Pain Med., [2]Neurosurg., [3]Neurol., Massachusetts Gen. Hosp., Boston, MA

Abstract: Neuroimaging and EEG studies suggest similarities between the sleeping brain and the anesthetized brain. Suppression of the cholinergic pathway of the ascending arousal system has been implicated in the regulation of states of consciousness during normal sleep-wake cycles as well as general anesthesia. Here we explore neuronal dynamics during dexmedetomidine (DEX) induced loss of consciousness versus natural sleep in the nucleus basalis of Meynert (NBM) and the dorsolateral prefrontal cortex (DLPFC). We performed simultaneous neural recordings from the NBM and the DLPFC in non-task performing primates. During each recording session, an IM dose of DEX was given to the animal after awake baseline data was collected. In addition, sleep recording experiments were performed at night (from 7pm) in order to acquire good natural sleep. While simultaneously acquiring extracellular data from the NBM and DLPFC, we performed standard EEG using non-invasive EEG electrodes on the scalp to identify sleep-wake cycles. Our preliminary results demonstrate a decrease in gamma and an increase in delta waves during natural sleep (NREM sleep) in both DLPFC and NBM. Interestingly, we found a more pronounced slow-wave delta in DLPFC when compared to the NBM. Coherence between DLPFC and NBM was significantly increased in the slow frequency, but decreased in the high frequency. During DEX-induced unconsciousness, there was a clear increase in coherence between NBM and DLPFC in the low frequency bands. In conclusion, our results demonstrate that neuronal dynamics changes in DLPFC and NBM are similar during sleep and DEX anesthesia. This may suggest overlying mechanisms of these different states of unconsciousness through the ascending cholinergic pathway to the neocortex.

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Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

Location: Hall A

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Program#/Poster#: 633.23/CC27

Topic: F.02. Animal Cognition and Behavior

Title: Alteration of NREM Sleep in mice with increased low-threshold burst firing in thalamocortical neurons

Authors: *J. HONG[1], J. LEE[2], G. HA[1], H.-S. SHIN[2], E. CHEONG[1];
[1]Yonsei Univ., Seoul, Korea, Republic of; [2]Inst. for Basic Sci., Daejeon, Korea, Republic of

Abstract: Sleep is composed of multiple states including non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep which have characteristic electroencephalogram (EEG), respectively. REM sleep displays low amplitude brain rhythms in theta frequency range (6-9Hz) and NREM sleep brain rhythms show high amplitude and multiple EEG patterns composed of slow wave (<0.5 Hz), delta wave (1-4 Hz) and spindle (7-14 Hz) by the frequency. The transition from wake to NREM sleep at the onset of sleep accompanies the dramatic change in brain rhythms in EEG from irregular and low amplitude pattern to relatively regular oscillatory and large amplitude pattern reflecting the synchronized thalamocortical oscillatory activity. Thalamocortical oscillations have been described to initiate from the intra-thalamic circuit composed of GABAergic thalamic reticular nucleus (TRN) neurons and glutamatergic thalamic cortical (TC) neurons and then to be transmitted to cortical neurons. Low-threshold burst firing of TC neurons mediated by T-type Ca2+ channels has been attributed in this phenomenon. However, the extents to which TC burst firing contribute to sleep architecture or sleep brain rhythms are not fully understood yet. Here we investigated the alteration of sleep patterns in mice with increased burst firing in TC neurons. Thalamic-restricted gene knockdown also displayed the alteration in NREM sleep confirming the role of TC burst firing in NREM sleep. We expect that this study could suggest the potential role of TC burst firing in the regulation of NREM sleep.

Disclosures: **J. Hong:** None. **J. Lee:** None. **G. Ha:** None. **H. Shin:** None. **E. Cheong:** None.

Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

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National Key Technology R&D Program of the Ministry of Science and Technology of China (2012BAI01B08)

Title: Two interneuron subtypes in laterodorsal tegmentum antagonistically control innate fear

Authors: *Y. HONGBIN[1], J. YANG[1], S. HAO[1], W. XI[1], X. HE[2], L. ZHU[1], H. LOU[1], Y. YU[1], F. XU[2], S. DUAN[1], H. WANG[1];
[1]Inst. of Neurosci., Zhejiang Univ., Zhejiang, China; [2]Inst. of Physics and Mathematics, wuhan, China

Abstract: Innate fear, induced by a threat such as the odor of a predator, plays a critical role in survival. Unlike conditioned fear, the neuronal circuitry underlying innate fear is largely unknown. Here, we discovered that the laterodorsal tegmentum (LDT) and lateral habenula (LHb) were specifically activated by the mouse predator odorant trimethylthiazoline (TMT). Using optogenetics to selectively stimulate GABAergic neurons in the LDT immediately produced fear-like responses (freezing, accelerated heart rate, and increased serum corticosterone), whereas prolonged stimulation caused anxiety-like behaviors. Interestingly, while selective stimulation of parvalbumin (PV)-positive interneurons similarly induced fear-like responses, stimulation of somatostatin-positive interneurons or inhibition of PV neurons in the LDT suppressed TMT-induced fear-like responses without affecting conditioned fear. Finally, activation of LHb glutamatergic inputs to LDT interneurons was sufficient to generate fear-like responses. Thus, the LDT plays an essential role in regulating innate fear and provides a potential target for therapeutic intervention for anxiety disorders.

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Poster

633. Functions of Prefrontal, Striatal, and Thalamic Circuits

Location: Hall A

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Topic: F.02. Animal Cognition and Behavior

Support: Canadian Institutes of Health Research

Title: Voluntary movement gates vestibular sensory coding in the ventral posterior lateral thalamus

Authors: *A. DALE, K. E. CULLEN;
Physiol., McGill Univ., Montreal, QC, Canada

Abstract: Successful navigation of the world around us is accomplished through precise coordination of our actions, and accurate perception of the motion we experience as a result of our own movements as well as occurrences in our environment. Vestibular system responses to self-motion are relayed through the thalamus to cortex where they contribute to higher-order processing. To date, the responses of neurons in the vestibular thalamus, specifically the ventral posterior lateral nucleus (VPL), have not been characterized during voluntary, natural movements in rhesus monkeys. Accordingly, here, we recorded from individual non-eye movement responsive VPL neurons during yaw rotations that were either passively applied or self-produced. In addition, we characterized responses to neck proprioceptive inputs to elucidate how this neuronal population integrates signals from multiple modalities. We found that neurons fell into two separate groups: approximately half encoded head-in-space (vestibular) motion while the other half were sensitive to both vestibular and neck proprioceptive signals, thereby providing an estimate of relative head and body motion. Moreover, all neurons showed dramatically reduced (nearly 90%) firing rate modulation in response to self-generated head motion relative to passive motion. Furthermore, during combined passive and active stimulation, the observed attenuation persisted such that neurons reliably encoded only the externally-generated component of the motion. Notably, VPL neurons encoded unexpected motion even more selectively than neurons in earlier stages of vestibular processing (vestibular nuclei: Roy and Cullen 2001; deep cerebellar nuclei: Brooks and Cullen 2013). Thus, our results demonstrate that ascending vestibular pathways through the thalamus carry a robust representation of unexpected self-motion, which is critical for ensuring perceptual stability during everyday behaviors.

Disclosures: **A. Dale:** None. **K.E. Cullen:** None.

Poster

634. Optogenetic and Chemogenetic Manipulation of Motivation and Emotion

Location: Hall A

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Topic: F.03. Motivation and Emotion

Support: EMBL

Swiss National Foundation

ERC Advanced Grant

Title: Loss of prefrontal control of a brainstem defensive behavior circuit following social defeat

Authors: *L. MARRONE, T. FRANKLIN, B. SILVA, C. GROSS;
EMBL, Monterotondo (RM), Italy

Abstract: The prefrontal cortex (PFC) is a brain area critical for behavioural flexibility and decision making in response to a changing environment and plays an important role in regulating emotions and moderating social behavior. It is known that the PFC exerts its functions through extensive connections with cortical and subcortical structures. Some of these structures are part of a network of brain regions associated with sociability, but the contribution of specific cortical-subcortical projections to social behavior has not yet been established. Using a model of repeated social defeat in mice, we investigated how projections from medial PFC (mPFC) to dorsal periaqueductal grey (dPAG), a structure involved in defensive behavior, play a role in behavioural adaptation to social threat. Using cholera toxin retrograde tracers and transgenic cell-type markers we showed that dPAG receives afferents exclusively from layer V mPFC excitatory neurons. Using *in vivo* local field potential recordings we found a decrease in functional connectivity between mPFC and dPAG in defeated mice and selective pharmacogenetic inhibition of mPFC-dPAG projections mimicked the behavioural adaptation to social defeat. These data suggest that mPFC projections exert inhibitory control over brainstem defensive circuits and are weakened during social defeat to adapt social behavior to the environment. To pinpoint the plasticity underlying this remodeling, we identified brain regions showing altered levels of several plasticity-associated molecules following social defeat. Immunostaining for pS6, a ribosomal protein whose phosphorylation reflects translational regulation, was decreased in the mPFC of defeated mice, suggesting that plasticity in mPFC may be involved in the behavioral remodeling. Currently, we are investigating changes in gene expression, cell morphology, and AMPA receptor subunit composition in mPFC-dPAG projecting neurons to identify the molecular mechanisms underlying the behavioral adaptation to social defeat.

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Poster

634. Optogenetic and Chemogenetic Manipulation of Motivation and Emotion

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Topic: F.03. Motivation and Emotion

Support: JPB Foundation

PIIF

PNDRF

JFDP

Whitehall Foundation

Klingenstein Foundation

NARSAD Younger Investigator Award

Title: Glutamatergic lateral hypothalamic inputs to VTA produce avoidance and suppress dopamine release in the nucleus accumbens

Authors: *E. NIEH, C. M. VANDER WEELE, K. N. PRESBREY, K. M. TYE;
Brain and Cognitive Sci., Picower Inst. For Learning and Memory, MIT, Cambridge, MA

Abstract: Recently we have shown that LH neurons sending projections to the VTA encode the learned action of seeking a reward, while LH neurons receiving projections from the VTA encode the conditioned and/or unconditioned stimuli. Activating the LH-VTA projection increases the willingness of mice to cross a shock floor to obtain sucrose rewards, while inhibiting the projection decreases this drive. After revealing that the LH sends both excitatory and inhibitory monosynaptic inputs onto both dopamine and GABA neurons in the VTA, we show that the inhibitory components are likely mediating the reward-seeking behavior while the excitatory components play a more modulatory role. Here, we show that activating the GABAergic component of the LH-VTA projection supports real-time place preference (n=6 ChR2, n=8 eYFP, **p=0.0025) and intracranial self-stimulation (***p=0.0009). In contrast, activating the glutamatergic component causes real-time place aversion (n=7 ChR2, n=6 eYFP, **p=0.0031). These data are contrary to the previous conceptualization of glutamatergic inputs from LH to VTA mediating positive reinforcement. In fact, it is quite surprising that inhibiting a projection to the VTA would be rewarding, while exciting it would be aversive, given the nature of dopamine neurons in the VTA. However, we used fast-scan cyclic voltammetry (FSCV) to measure the effects of activating the GABAergic LH component on dopamine release in the nucleus accumbens (NAc) and find that it increases dopamine release (n=2 mice, 20 trials each;

***p<0.0001). Meanwhile, activating the glutamatergic component of the LH-VTA projection decreases dopamine release (n=3 mice, 20 trials each; ***p<0.0001). Together these data suggest that the LH promotes and suppresses the release of dopamine in the NAc via the disinhibition of dopamine neurons in the VTA.

Disclosures: E. Nieh: None. **C.M. Vander Weele:** None. **K.N. Presbrey:** None. **K.M. Tye:** None.

Poster

634. Optogenetic and Chemogenetic Manipulation of Motivation and Emotion

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Topic: F.03. Motivation and Emotion

Support: New York Stem Cell Foundation

JPB Foundation

PIIF

PNDRF

JFDP

Whitehall Foundation

Klingenstein Foundation

Title: Observing and controlling projection-defined medial prefrontal cortex subpopulations in reward and aversion

Authors: *C. M. VANDER WEELE[1], R. WICHMANN[1], I. C. ESPINEL[1], E. H. S. SCHUT[2], E. IZADMEHR[1], C. E. WILDES[1], K. M. TYE[1];
[1]Brain and Cognitive Sci., MIT, Cambridge, MA; [2]Donders Inst., Radboud Univ., Nijmegen, Netherlands

Abstract: The medial prefrontal cortex (mPFC) has been implicated in higher order cognitive functions and coordinates the execution of motivated behaviors though its projections to downstream targets. However, how mPFC neurons that project to different downstream targets represent and coordinate motivated behaviors is unclear. Our goal is to understand how mPFC

neuronal subpopulations encode stimulus valence and where this information is communicated downstream to instigate adaptive behavioral responses, such as approach or avoidance. Using *in vivo* freely-moving calcium imaging enabled by a genetically-encodable calcium indicator (GCaMP6m), we explored the real-time neural dynamics in the mPFC during exposure to innately appetitive and aversive olfactory stimuli. We have found that the mPFC neurons have diverse response profiles. Approximately 50% of neurons (n = 273) responded similarly, perhaps encoding general salience. ~26% showed selective responding to only one of the stimuli. Another subset of mPFC neurons (~19%) showed opposing responses, characterized by increased activity to one stimulus and decreased activity to the other. mPFC neurons encoding positive or negative valence likely have distinct downstream targets. The periaqueductal gray (PAG) is has been linked to aversive behaviors and we have found that optogenetic activation of mPFC terminals in the PAG produces avoidance (n = 6 ChR2, p = 0.01) and anxiety-related behaviors (p = 0.04). Further, stimulation of this pathway evokes defensive (p = 0.03) and escape (p = 0.01) behaviors in the marble burying assay, suggesting that stimulation of the mPFC:PAG circuit triggers active avoidance behaviors. These effects were not observed in control animals (n = 6 eYFP; p > 0.05). The paraventricular nucleus of the thalamus (PVT) has been implicated in reward, and receives dense input from the mPFC. To selectively manipulate mPFC neurons terminating in PVT, we used an anterogradely traveling viral vector carrying ChR2 in a double inverted open reading frame in the mPFC and a retrogradely traveling viral vector carrying cre-recombinase in the PVT. In animals expressing ChR2 only in neurons originating in the mPFC and terminating in the PVT, we show that activation of the PVT-projecting mPFC neurons is positively reinforcing (n = 3 ChR2, p = 0.04); an effect not observed in controls (n = 3 eYFP; p > 0.05). Together, these data suggest that the mPFC controls avoidance and approach behaviors through its projections to the PAG and PVT, respectively. Our results advance us towards a circuit-level explanation for how the mPFC can exert control over valence-defined motivated behaviors.

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Poster

634. Optogenetic and Chemogenetic Manipulation of Motivation and Emotion

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Topic: F.03. Motivation and Emotion

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JPB Foundation

Picower Institute Innovation Fund (PIIF)

PNDRF

JFDP

Whitehall Foundation

Klingenstein Foundation

Title: Retrieval of positive and negative associations produces opposite responses in BLA neurons projecting to NAc and CeM

Authors: *A. BEYELER, P. NAMBURI, C. SIMONNET, G. F. GLOBER, G. F. CONYERS, R. LUCK, C. P. WILDES, K. M. TYE;
Brain and Cognitive Sci., Picower Insitute for Learning and Memory, MIT, Cambridge, MA

Abstract: The ability to process positive and negative emotional valence guides our daily life, allowing us to produce adaptive behaviors in order to ensure our survival and well-being. The basolateral amygdala (BLA) is necessary for processing associative memories of both positive and negative valence. However, the natural encoding dynamics of BLA neurons with specific downstream targets has not been explored. By combining optogenetic photo-identification of BLA neurons with a specific projection target and large-scale electrophysiological recordings in behaving mice, we tested whether BLA neurons projecting to different downstream targets encode valence differently. After mice learned to associate an auditory cue with a rewarding outcome (sucrose delivery), and a second tone with an aversive outcome (quinine delivery), we recorded BLA neurons while the animals were performing the task. Of the 993 single units we recorded in the BLA, 53% responded to cues of positive and/or negative valence. Units photo-identified as projecting to the nucleus accumbens (25 NAc projectors, n=5 mice) were either 1) excited by cues of positive valence or 2) inhibited by cues of negative valence. Conversely, BLA neurons projecting to the medial division of the central amygdala (35 CeM projectors, n=3 mice) were either 1) excited by cues of negative valence or 2) inhibited by cues of positive valence. Both NAc- and CeM-projecting BLA neuron populations also had some cells that responded to both cues. In contrast to the conditioned valence-specific encoding properties of BLA-NAc and BLA-CeM populations, BLA units photo-identified as projecting to the ventral hippocampus (33 vHPC projectors, n=3 mice) showed a similar distribution of responses compared to the entire BLA population. These results support a model where NAc and CeM projectors provide valence-specific excitation to their downstream target during cues of positive and negative valence, respectively, and provide inhibition during cues of opposite valence. The mutually exclusive pattern of coding of the NAc and CeM projectors also suggests that these two populations may engage in reciprocal inhibition.

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Poster

634. Optogenetic and Chemogenetic Manipulation of Motivation and Emotion

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Whitehead Career Development Chair

Whitehall Foundation

Klingenstein Foundation

New York Stem Cell Foundation

Title: Amygdala-prefrontal interactions during the competition of fear- and reward-related memories

Authors: *A. BURGOS-ROBLES, M. ANAHTAR, K. M. TYE;
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Abstract: In nature, environmental stimuli signaling positive or negative outcomes may be presented simultaneously, forcing animals to choose behavioral responses that may be in competition with each other. However, the neural mechanisms underlying the competition, coordination or selection of opposing motivated behaviors (reward-seeking and freezing) are not well understood. In this study, we use multichannel single-unit recordings and optogenetic manipulations in freely-moving rats to examine functional interactions between the basolateral amygdala (BLA) and the prelimbic cortex (PL), which are two highly interconnected structures that have been widely implicated in various fear and reward conditioning tasks. We have detected in both structures populations of neurons that exhibit phasic changes in firing to cues that predict either footshocks (BLA: 11/110, 10%; PL: 12/76, 16%) or sucrose (BLA: 9/110, 8%; PL: 14/76, 18%). We also observe cells that exhibit the same response (BLA: 15/110, 14%; PL:

22/76, 30%) or opposite responses (BLA: 13/110, 12%; PL: 7/76, 9%) to the fear and reward cues. Cross-correlation analysis shows strong correlated activity between the BLA and PL during the presentation of both fear and reward cues. We are using optogenetic-mediated stimulation or inhibition to determine whether BLA-PL interactions play a functional role in the modulation of cue-evoked fear and reward-seeking. Photostimulation reduces the latency to conditioned freezing when rats are challenged by the simultaneous presentation of the fear and reward cues ("competition trials"; Laser-OFF: 7.7 s, Laser-ON: 2.8 s, $p = 0.0043$). Despite shorter latency to freezing, the total percentage of time that rats spend freezing during the cue presentation is unaffected by BLA-PL stimulation ("fear trials", OFF: 59%, ON: 58%, $p = 0.74$; "competition trials", OFF: 8%, ON: 11%, $p = 0.52$). Meanwhile, stimulation of BLA terminals in PL does not significantly affect the latency for sucrose-port entry ("reward trials", OFF: 3.8 s, ON: 3.1 s, $p = 0.46$; "competition trials", OFF: 3.6 s, ON: 4.1 s, $p = 0.76$), nor does it affect the total time that rats spend in the port collecting sucrose ("reward trials", OFF: 62%, ON: 63%, $p = 0.69$; "competition trials", OFF: 60%, ON: 57%, $p = 0.75$). Together these preliminary results suggest that BLA projections to PL promote faster expression of conditioned fear when environmental stimuli of opposite valence are competing to drive behavioral responses.

Disclosures: **A. Burgos-Robles:** None. **M. Anahtar:** None. **K.M. Tye:** None.

Poster

634. Optogenetic and Chemogenetic Manipulation of Motivation and Emotion

Location: Hall A

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Topic: F.03. Motivation and Emotion

Support: NIH Grant K99/R00AA021782

NIH Grant R01AA12882

Title: Subregions of the thalamic paraventricular nucleus make distinct contributions to emotional behavior

Authors: *J. R. BARSON[1,2], S. F. LEIBOWITZ[2];
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Abstract: Background: The paraventricular nucleus of the thalamus (PVT) is a limbic region thought to play a role in emotional behavior. With recent studies showing the anterior (aPVT)

and posterior (pPVT) areas of this nucleus to have different roles in consummatory behavior, the present study investigated whether these subregions also make different contributions to emotional behaviors. Methods: Adult male Long-Evans rats with cannulas aimed at the aPVT or pPVT were microinjected in a between-subject design with the GABA(B)+GABA(A) agonists baclofen+muscimol (0.3+0.03 nmol) or saline vehicle (0.3 ul) (n=7-8/injection/area) and tested 5 minutes post-injection. On separate days, they were tested in a novel open field (15 min); then after three additional daily exposures in a familiar open field (15 min); and then one week later in an elevated plus maze (5 min). The order of injections was counterbalanced for each subject. Results: In the novel open field, inactivation with GABA agonists of the aPVT and pPVT significantly reduced locomotor activity (as measured by ambulatory distance, time, counts, and episodes, average and total velocity, and vertical counts), with this effect somewhat stronger after pPVT inactivation. In the familiar open field, inactivation of these subregions also caused a significant reduction in locomotor activity, which was similar in magnitude for both the aPVT and pPVT. This is in contrast to anxiety-like behavior in the elevated plus maze, which was significantly increased (as measured by reduced open arm time and entries) by inactivation only of the pPVT, with locomotor activity in the plus maze (closed arm entries) otherwise unaffected. Conclusions: These results suggest that, while both PVT subregions are necessary for locomotor activity in a familiar environment, the pPVT has an additional function in novelty-induced locomotor activity and is necessary for the expression of anxiety-like behavior, indicating that this subregion plays a greater role in reacting to aversive stimuli. These changes in emotional behaviors induced by inhibitory GABA agonists in the pPVT were somewhat unexpected, in light of other evidence showing an excitatory neurochemical, orexin/hypocretin, to have the same effects in the pPVT. With prior studies also showing GABA and orexin/hypocretin in the pPVT to be similar in promoting food intake, the present results suggest that different neurochemical pathways from the pPVT can impact a specific behavior in similar ways. Taken together, these findings support a role for the PVT in the expression of emotional behavior and show for the first time that its subregions make distinct contributions to this activity.

Disclosures: **J.R. Barson:** None. **S.F. Leibowitz:** None.

Poster

634. Optogenetic and Chemogenetic Manipulation of Motivation and Emotion

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Title: Differential activity in afferents to the paraventricular nucleus of the thalamus in response to incentive and predictive stimuli

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Abstract: Cues that are repeatedly paired with rewards can acquire predictive value, guiding behavior towards valuable resources in the environment (e.g. food, water, etc.). However, reward-paired cues can also acquire incentive value (i.e. incentive salience), and can come to control behavior, often to the point that it becomes maladaptive. Until recently, it was difficult to study the neural circuitry underlying the attribution of incentive salience to reward-paired cues, since it was assumed that the incentive and predictive values of cues were acquired simultaneously. However, using an animal model that captures individual variation in response to discrete reward-paired cues, we are now able to parse these properties of stimulus-reward learning. When rats are exposed to a Pavlovian conditioning paradigm, wherein a discrete cue predicts food reward, some rats, termed sign-trackers (STs), attribute both predictive and incentive value to the cue. Other rats, termed goal-trackers (GTs), treat the cue exclusively as a predictor of impending reward delivery. Previous studies from our laboratory have highlighted the paraventricular nucleus of the thalamus (PVT) as a critical component of the neural circuitry mediating these behaviors. Here, we sought to explore the engagement of PVT circuitry in sign- and goal-tracking behaviors. The retrograde tracer Fluoro-Gold (FG) was injected into the PVT and levels of cue-induced neuronal activity were assessed by quantifying the amount of c-fos in FG-expressing cells. This technique allows us to assess differences in activation between STs and GTs specifically in afferents to the PVT. We were especially interested in examining activity in the medial prefrontal cortex, since previous studies from our lab have suggested that prelimbic cortical afferents to the PVT are involved in mediating goal-tracking behavior. As predicted, results show that, relative to STs, GTs have increased cue-induced cortical activation, specifically in prelimbic and infralimbic neurons that project to the PVT. There we no significant ST/GT differences in neuronal activation in hypothalamic brain areas that project to the PVT, including the dorsomedial nucleus and lateral hypothalamic nucleus. These results demonstrate that sign- and goal-tracking behaviors engage distinct neural circuits projecting to the PVT in response to cue presentation, and support the hypothesis that GTs have greater cortical-control of their behavior. Ongoing analyses will further explore activity in different afferent projections to the PVT, including the insular cortex and central amygdala, as well as PVT efferents to the nucleus accumbens and extended amygdala.

Disclosures: J.L. Haight: None. **S.B. Flagel:** None.

Poster

634. Optogenetic and Chemogenetic Manipulation of Motivation and Emotion

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Topic: F.03. Motivation and Emotion

Support: NIH/NIDA R01 DA038599

Title: Chemogenetic manipulations of prelimbic inputs to the paraventricular nucleus of the thalamus alter sign- and goal-tracking behavior

Authors: *I. RIVERO-COVELO[1], J. L. HAIGHT[1], K. M. FRASER[1], B. N. KUHN[1], S. M. FERGUSON[2], S. B. FLAGEL[1];
[1]The Mol. and Behavioral Neurosci. Inst., Univ. of Michigan, Ann Arbor, MI; [2]Ctr. for Integrative Brain Res., Seattle Children's Res. Inst., Seattle, WA

Abstract: Environmental cues that predict the presence of natural rewards (e.g. food or sex) can acquire incentive motivational value in addition to predictive value. Notably, cues that acquire incentive motivational value can gain inordinate control over behavior, often leading to maladaptive tendencies such as overeating or drug addiction. When rats are exposed to a Pavlovian conditioned approach task, in which the presentation of a lever precedes the presentation of a food reward, some rats, termed sign-trackers (STs), approach the lever; while other rats, termed goal-trackers (GTs), approach the food cup. Thus, for STs, the cue becomes an incentive stimulus; whereas for GTs it is just a predictor. Recently, we have shown that the paraventricular nucleus of the thalamus (PVT) is involved in the regulation of sign- vs. goal-tracking behavior. Selective lesions of the PVT enhance sign-tracking behavior in both STs and GTs, but may serve distinct functions in these two phenotypes. Relative to GTs, STs show enhanced c-fos expression in the PVT in response to a discrete cue that has been previously paired with food- or drug-reward. Further, for STs, cue-induced c-fos levels in the PVT correlate with cue-induced c-fos in subcortical regions; whereas for GTs, cue-induced c-fos in the PVT correlates with the prelimbic cortex (PrL). Thus, we postulate that the PVT may act as a node for the attribution of incentive motivational value to reward cues in STs, and that inputs to the PVT from the PrL may serve to inhibit this process in GTs. Here, we interrogated the role of this circuit in sign- and goal-tracking behaviors using a dual viral vector approach to selectively express Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in projection neurons from the PrL to the PVT. A Cre-dependent flip-excision AAV viral vector expressing inhibitory Gi/o- or stimulatory Gq-coupled DREADDs was infused into the PrL of GTs and STs, respectively, while a CAV-Cre viral vector was injected into the PVT. This resulted in Gi/o-

DREADD expression in PrL-PVT neurons in GTs, and Gq-DREADD expression in STs. Activation of Gi/o-DREADDs via systemic administration of clozapine N-oxide (CNO) inhibited the PrL-PVT circuit in GTs, and resulted in an increase in sign-tracking behavior. Conversely, in STs, CNO-induced stimulation of Gq signaling in PrL-PVT neurons increased goal-tracking behavior. Thus, "turning off" the PrL-PVT circuit leads to sign-tracking behavior in GTs, while "turning on" the PrL-PVT circuit induces goal-tracking behavior in STs. Top-down processes from the PrL to the PVT may therefore be a critical component of the circuitry that goes awry in addiction and related disorders.

Disclosures: I. Rivero-Covelo: None. **J.L. Haight:** None. **K.M. Fraser:** None. **B.N. Kuhn:** None. **S.M. Ferguson:** None. **S.B. Flagel:** None.

Poster

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Title: A population of parvalbumin-expressing (pv+) neurons in the lateral habenula promotes anxiety

Authors: *L. POZZI, I. PALLUCCHI, I. LAZARIDIS, I. POLLAK DOROCIC, K. MELETIS; Karolinska Institutet, Stockholm, Sweden

Abstract: Dysfunction in GABAergic parvalbumin-expressing (PV) interneurons has been implicated in the pathogenesis of various neuropsychiatric disorders including anxiety. Neurons in lateral habenula (LHb) respond to punishment and aversive stimuli, and this circuit has been implicated in mood disorders. The neuron subtypes present in LHb and how they contribute to discrete aspects of emotional behavior has not been determined. We have identified a population of PV-expressing neurons in the LHb that promotes anxiety-like behaviors. Genetic targeting (AAV DIO GFP) of the LHb in Vglut2-Cre and Vgat-Cre mice revealed that LHb PV+ neurons express both glutamatergic (30% Vglut2) and GABAergic (20% Vgat) markers. We further used optogenetics in PV-Cre mice to selectively activate PV+ neurons in the LHb (AAV DIO ChR2-mCherry) and to investigate their functional role in modulation of anxiety-like behaviors in the open field and the elevated plus maze. We found that photoactivation of LHb PV+ neurons induced anxiety-like behavior. In the open field, optogenetic stimulation resulted in a significant

decreased in the time spent in the center. Similarly, in the elevated plus maze optogenetic stimulation of LHb PV+ neurons resulted in a significant decrease the time spent in the open arms. These findings expand our understanding of the diversity of neuronal populations in the LHb and provide a foundation for investigating the role of LHb PV+ neurons in anxiety.

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Poster

634. Optogenetic and Chemogenetic Manipulation of Motivation and Emotion

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Topic: F.03. Motivation and Emotion

Title: Ventral striatal projections to the lateral habenula modulate aggression reward

Authors: *S. A. GOLDEN[1], M. HESHMATI[2], D. J. CHRISTOFFEL[3], K. GUISE[2], M. L. PFAU[2], H. ALEYASIN[2], G. E. HODES[2], M. FLANIGAN[2], D. BREGMAN[2], L. KHIBNIK[2], J. TAI[2], N. REBUSI[2], N. REBUSI[2], B. KRAWITZ[2], D. CHAUDHURY[2], J. J. WALSH[3], Y. SHAHAM[1], M.-H. HAN[2], M. L. SHAPIRO[2], S. J. RUSSO[2];
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Abstract: Maladaptive aggressive behavior is associated with a number of neuropsychiatric disorders and is thought to result, in part, from inappropriate activation of brain reward systems in response to aggressive or violent social stimuli. A series of nuclei within the ventromedial hypothalamus, extended amygdalar and limbic circuits are known to encode the initiation of aggression; however, little is known about the neural circuit mechanisms that directly modulate the motivational or rewarding component of aggressive behavior11. To address this question, we established a mouse behavioral model to measure the valence of aggressive inter-male social interaction with a smaller 6-8 week old subordinate intruder as reinforcement for the development of conditioned place preference (CPP). In this model, aggressors (AGG) develop a CPP, while non-aggressors (NON) develop a conditioned place aversion (CPA), to the intruder-paired context. Further, we identify a dopamine receptor 2-containing GABAergic medium spiny neuron projection from the ventral striatum (vStr) to the lateral habenula (lHb) that bi-directionally controls the valence of intruder interactions. Circuit-specific optogenetic silencing of inhibitory GABAergic vStr-lHb terminals of AGG with halorhodopsin (NpHR3.0) increases lHb neuronal firing and abolishes CPP to the intruder-paired side. Conversely, activation of

GABAergic vStr-lHb terminals of NON with channelrhodopsin (ChR2) decreases lHb neuronal firing and promotes CPP to the intruder-paired side. Lastly, we show that inhibitory transmission at vStr-lHb terminals do not control the initiation of aggressive behavior in NON, but rather modulates the intensity of aggression in AGG. These results demonstrate that the vStr-lHb circuit plays a critical role in regulating the valence of inter-male aggressive behavior, and provide novel mechanistic insight into the neural circuits modulating aggression reward processing.

Disclosures: **S.A. Golden:** None. **M. Heshmati:** None. **D.J. Christoffel:** None. **K. Guise:** None. **M.L. Pfau:** None. **H. Aleyasin:** None. **G.E. Hodes:** None. **M. Flanigan:** None. **D. Bregman:** None. **L. Khibnik:** None. **J. Tai:** None. **N. Rebusi:** None. **N. Rebusi:** None. **B. Krawitz:** None. **D. Chaudhury:** None. **J.J. Walsh:** None. **Y. Shaham:** None. **M. Han:** None. **M.L. Shapiro:** None. **S.J. Russo:** None.

Poster

634. Optogenetic and Chemogenetic Manipulation of Motivation and Emotion

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Topic: F.03. Motivation and Emotion

Support: Svenska Sällskapet för Medicinsk Forskning (SSMF)

Title: Pyramidal cells-OLMα2 interneurons network underlies theta activity and anxiety related behavior in the ventral hippocampus

Authors: S. MIKULOVIC[1], *C. RESTREPO[1], S. PUPE[2], A. TORT[4], K. KULLANDER[3], R. LEÃO[3];
[1]Uppsala Univ., Uppsala, Sweden; [2]Neurosciences, [3]Dept. of Neurosci., Uppsala university, Uppsala, Sweden; [4]2.Brain Institute, Federal Univ. of Rio Grande do Norte, Natal-RN, Brazil

Abstract: Theta oscillations in the dorsal hippocampus are described as one of the most prominent rhythms of the brain. This 4-12 Hz have been associated with multiple behaviors, especially with movement. Differentially, theta activity in the ventral hippocampus has been implicated in emotions related behavior. It was suggested that specific GABAergic interneuron subtypes play differential roles in driving hippocampal oscillations. Although different populations of hippocampal interneurons fire preferentially to specific phases of theta, phase-locking firing itself does not prove a causal role in theta generation. We found a specific subtype of oriens lacunosum-moleculare (OLM) interneurons expressing Chrna2 receptor differentially distributed along the dorso-ventral hippocampal axis. Using optogenetic tools in anesthetized and

freely moving animals, we found that activation of this population induce prominent theta activity in the ventral but not in the dorsal hippocampus. This circuit includes pyramidal cells activity. Interestingly, the induced theta rhythm was not correlated with animals' movements. In addition, we found that this induced theta activity regulates anxiety related behavior. Taken together, our results provide the first evidence of a single morphologically defined cell population which in a network including pyramidal cells causally drives ventral hippocampal theta oscillations.

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Poster

634. Optogenetic and Chemogenetic Manipulation of Motivation and Emotion

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Topic: F.03. Motivation and Emotion

Title: Dissection of social neurocircuitry using chemogenetics and pharmaco-MRI

Authors: ***M. BENEKAREDDY**, M. SAXE, M. VON KIENLIN, B. KUENNECKE, A. GHOSH;
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Abstract: Neurodevelopmental disorders like autism spectrum disorders and schizophrenia are often characterized by marked impairments in social function. The brain regions responsible for generating social behavior are currently not well understood. The prefrontal cortex (PFC) has been highlighted as an important node in the 'social brain' network. In this study, we used a combination of chemogenetics and rodent social behavior tasks, to assess the consequences of altered neural activity in the PFC on social behavior in rats and mice. Further, using pharmacological magnetic resonance imaging (phMRI) methods, we identify a network of brain regions associated with socially-directed behavior. Acute activation of the PFC using hM3D (a Gq-protein-coupled chemogenetic neural activator) in excitatory neurons led to a reversible decrease in sociability in both rats and mice. Chronic perturbation of PFC activity with expression of either hM3D in excitatory neurons or with hM4D (a Gi-protein-coupled chemogenetic neural inhibitor) in parvalbumin or somatostatin inhibitory neuronal subtypes altered social function in a time-dependent and cell-type-dependent manner. In a further effort to investigate the brain-wide consequences of activating the PFC, animals were subjected to MRI

during chemogenetic activation. Activation of the PFC using hM3D led to a significant increase in blood perfusion in the PFC and in other brain regions including nucleus accumbens, and the dorsal raphe nucleus. Our results suggest that reciprocal connections between PFC and several key subcortical regions provide a circuit level framework for altered cortical and sub-cortical function to modify social behavior.

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Poster

634. Optogenetic and Chemogenetic Manipulation of Motivation and Emotion

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Title: Characterizing behavior-suppressing circuits: optogenetic stimulation of basal amygdala terminals in nucleus accumbens shell suppresses cue-evoked seeking and drinking

Authors: *Z. MILLAN, P. H. JANAK;
Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD

Abstract: The nucleus accumbens shell strongly inhibits feeding during satiety, reward seeking in the presence of an unrewarded cue, and drug seeking following its extinction. Understanding the mechanisms that promote suppressive control over motivated behavior has important implications for pathologies such as drug addiction and binge-eating disorders, which are characterized by a significant loss of control over seeking and consumption. Here we used an optogenetic approach to examine basal amygdala (BA) projections that target the accumbens shell [NAc(shell)] and whether stimulation of a BA-to-NAc(shell) pathway might be sufficient to suppress conditioned behavior evoked by either alcohol- or sucrose-predictive cues. Rats in the alcohol study received intermittent homecage access to EtOH (15%v/v) followed by Pavlovian conditioning of a 10s auditory cue paired with delivery of EtOH (15% v/v). Rats in the sucrose study received Pavlovian conditioning as above, reinforced with sucrose (10%v/v). On test, rats were assessed for cue-evoked seeking in the presence of both non-reinforced and reinforced

reward cues. We found that stimulation of BA terminals in NAc(shell) during reward cue presentations impaired conditioned port entries under non-reinforced or reinforced test conditions. Importantly, when cue-associated EtOH or sucrose was delivered at the offset of optical stimulation, rats maintained their ability to port entry. This latter finding suggests that the suppressing effect of stimulation on conditioned behavior is well-timed to the duration of stimulation. Finally, we examined whether the inhibitory effect of BA-to-NAc(shell) stimulation could also accutely interrupt licking during bouts of alcohol or sucrose drinking. Rats were placed on a 10 min homecage access regime prior to stimulation test. We confirmed the ability of this pathway to suppress drinking behavior. Together, these findings suggest that optogenetic stimulation of a BA-to-NAc(shell) pathway is sufficient to disrupt both conditioned and unconditioned reward-motivated behaviors.

Disclosures: Z. Millan: None. **P.H. Janak:** None.

Poster

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Topic: F.03. Motivation and Emotion

Title: Are the auditory pathways converging in the Lateral Amygdala required for the expression of Pavlovian defense reactions?

Authors: *L. DIAZ-MATAIX[1], N. BENABDALLAH[1], S. A. SERKA[1], V. DOYERE[2,1], J. E. LEDOUX[1,3];
[1]Ctr. for Neural Sci., New York Univ., New York, NY; [2]Cognition and Behavior, Paris-Saclay Inst. of Neurosci. (Neuro-PSI), Orsay, France; [3]Ebi, Nathan Kline Inst., Orangeburg, NY

Abstract: In Pavlovian auditory threat conditioning the conditioned stimulus (CS) arrives to the Lateral Nucleus of the Amygdala (LA) through two main brain pathways: a direct thalamo-amygdala, and an indirect thalamo-cortico-amygdala connection. The acoustic stimulus arrives to the medial areas of the auditory thalamus composed by the Medial Geniculate Nucleus (MGm) and the Post Intralaminar Nucleus (PIL), and from these nuclei projections is sent to the LA. The CS can also reach the LA through a pathway from the auditory thalamus to the primary auditory cortex (Temporal Associatin Cortex area TE1) which in the rat projects to TE3, and from there to the LA. Either of these two pathways (thalamo- and cortico-amygdala) is sufficient to mediate threat conditioning (Romanski & LeDoux., 1992; LeDoux., 1995). Electrophysiological studies show that threat learning induces persistent enhanced synaptic plasticity in both cortico and

thalamo-amygdala pathways (Tsvetkov et al., 2002; Rogan et al., 1997). Although the contribution of these auditory pathways to threat learning has been extensively studied, little is known about their role in the expression of threat memories. By using chemogenetics we examined the contribution of these auditory pathways to the expression of learned defense responses to a pure tone. MGm/PIL or TE3 was infected with virus carrying inhibitory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). After 6 weeks cannulae were implanted bilaterally into LA with a stainless steel recording electrode attached to the left cannula. Rats were habituated to the CS and context before conditioning them by presenting 3 tone (CS)-shock (US) pairings. Long-term memory tests were performed by presenting 5 unreinforced CSs after intra-LA infusion of the DREADD agonist CNO (Clozapine-N-oxide) or vehicle in the same animals in a counterbalanced manner to allow within animal comparison. The inactivation of the thalamic terminals in the LA by the infusion of CNO impairs freezing in parallel with a decrease in the amplitude of the LA auditory field evoked potential. Ongoing experiments are being conducted to elucidate the role of auditory cortex on threat memory expression. So far, the results suggest the necessity of an intact and functional thalamo-amygdala circuit for the expression of previously learned defense responses.

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Poster

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Vertex Scholar Award

OHSU Brian Institute Fellowship

Title: An extended amygdala to ventral tegmental area circuit underlies ethanol-seeking behavior in mice

Authors: *M. M. PINA[1], C. L. CUNNINGHAM[2];
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Abstract: Associations between external stimuli and abused drugs contribute to relapse to use by eliciting craving and driving subsequent drug seeking. The bed nucleus of the stria terminalis (BNST) is an extended amygdala structure that appears to underlie drug-seeking behavior. Anatomically, the BNST send a dense set of projections to the ventral tegmental area (VTA), a region critically involved in motivated behavior. Behaviorally, BNST inhibition disrupts stress- and cue-induced drug seeking. Importantly, BNST disconnection from the VTA has been shown to significantly attenuate cue-induced cocaine seeking, as measured by conditioned place preference (CPP). Though indirect, this evidence indicates that a projection from the BNST to the VTA may underlie cue-induced drug seeking. In the present experiments, we used selective manipulations to directly establish a role for the BNST and its VTA projections in cue-induced ethanol seeking behavior in adult male DBA/2J mice. An unbiased CPP procedure was used, where ethanol (2 g/kg, IP) was given immediately before exposure to a distinct tactile cue and an expression (seeking) test was given 24 h after the final conditioning session. In experiment 1, we gauged the BNST's ability to regulate ethanol CPP expression using virally-expressed inhibitory designer receptors (i.e., Gi-DREADDs). Stimulation of Gi-DREADDs by injection of clozapine-N-oxide (CNO; 10 mg/kg, IP) 30 min before the expression test significantly disrupted ethanol CPP. In experiment 2, an intersectional approach was used to selectively express Gi-DREADDs in BNST-VTA projection neurons. Silencing of BNST-VTA neurons by CNO (as in exp. 1) abolished ethanol CPP entirely. Control studies show that these results were not due to a direct effect of CNO, as CNO (10-20 mg/kg) did not affect ethanol CPP expression or test activity in the absence of Gi-DREADDs. Our findings suggest that a BNST-VTA circuit is required for the expression of ethanol-seeking behavior, as indexed by CPP. Moreover, our work complements and expands upon previous findings and provides novel evidence for a direct BNST input to VTA in cue-induced ethanol seeking. Taken together with the existing literature, these studies indicate that the BNST and its projections to VTA are promising neural targets for treatments directed at reducing craving and relapse.

Disclosures: **M.M. Pina:** None. **C.L. Cunningham:** None.

Poster

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Title: Mesointerpeduncular circuitry and dopaminergic control of affective state

Authors: *S. R. DEGROOT, R. ZHAO-SHEA, P. GARDNER, A. TAPPER;
UMASS Med. Sch., Worcester, MA

Abstract: Anxiety disorders are the most common class of mental disorders. Anxiety is an affective state classically governed by the prefrontal cortex, hippocampus, and the extended amygdala, which includes the bed nucleus of the stria terminalis (BNST). Previous studies suggest that stimulation of glutamatergic BNST efferents in the ventral tegmental area (VTA) is anxiogenic. Further, the VTA can exhibit control of affective state by heterogeneous efferent terminal activation in certain brain regions. Recently, we showed that the mesointerpeduncular circuit, which consists of VTA dopaminergic (DAergic) neurons that innervate the interpeduncular nucleus (IPN), is an important component in nicotine withdrawal-induced anxiety. The current study further explores the mesointerpeduncular circuitry, specifically DAergic control of the IPN in drug naïve mice. Using cell-attached patch-clamp electrophysiology in acute mouse brain slices, we defined two neuronal populations of the ventral IPN by input resistance and response to exogenous application of DA. Type A neurons have low input resistance and respond to DA with an increase in spontaneous action potential frequency (sAPF), while Type B neurons exhibit a higher input resistance and respond to DA with a decrease in sAPF. DA only affected sAPF in the ventral half of the IPN and the dorsal lateral subnucleus with little effect in the rostral IPN. Using viral mediated gene delivery and CRE-Lox technology, we expressed channelrhodopsin-2 (ChR2) specifically in putative DAergic VTA neurons of tyrosine hydroxylase (TH)-CRE mice. Fluorescence microscopy revealed VTA terminals located specifically in regions of the IPN where DA modulated sAPF. Light stimulation of VTA IPN afferents resulted in modulation of sAPF consistent with exogenous DA application. D1-family DA receptor antagonists blocked the main effect of ChR2 stimulation and DA-induced changes in sAPF. Whole-cell patch clamp recordings revealed changes in excitatory postsynaptic current frequency, but not amplitude in IPN neurons during VTA terminal stimulation suggesting that DA acts presynaptically to modulate IPN inputs. Our study further characterizes the mesointerpeduncular circuit, which may play a critical role in affective behavior.

Disclosures: **S.R. Degroot:** None. **R. Zhao-Shea:** None. **P. Gardner:** None. **A. Tapper:** None.

Poster

634. Optogenetic and Chemogenetic Manipulation of Motivation and Emotion

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 634.17/CC46

Topic: F.03. Motivation and Emotion

Title: Structure and function of circuits that provide input to dopaminergic and serotonergic neurons

Authors: *I. POLLAK DOROCIC, D. FÜRTH, Y. XUAN, K. MELETIS;
Dept. Neurosci., Karolinska Institutet, Stockholm, Sweden

Abstract: New genetically-restricted transsynaptic tracing strategies allow us to dissect neural circuits in unprecedented detail. Our aim is to define circuits that provide direct inputs to dopaminergic, serotonergic and GABAergic neurons, focusing on striatum-projecting cells, and to probe those circuits functionally. Here, we employ a genetically modified rabies virus in transgenic mice to selectively map monosynaptic inputs to striatum-projecting dopaminergic and GABAergic cells in the ventral tegmental area (VTA) and substantia nigra (SN) region as well as striatum-projecting serotonergic and GABAergic cells in the dorsal raphe nucleus (DR) region. To obtain selective targeting of specific cell types, we first injected a Cre-dependent adeno-associated virus containing TVA receptor and rabies glycoprotein into the VTA/SN region of TH-Cre and Vgat-Cre animals, and into the DR region of SERT-Cre and Vgat-Cre animals, respectively. Subsequently, Rabies-EGFP was injected into the striatum and is taken up only by the TVA-expressing axons of the projection neurons. Rabies-EGFP retrogradely crosses one synapse into the presynaptic partners of the projection neurons. Using this strategy we were able to localize and characterize the specific brain-wide input neurons to only striatum-projecting dopaminergic, serotonergic and GABAergic cells. One region found to have prominent input to dopaminergic cells of the VTA and serotonergic cells of the DR is the lateral habenula (LHb), a region involved in negative reinforcement. In order to functionally probe this input population, we used a variant of the transgenic rabies virus, which contains the excitatory opsin channelrhodopsin (Rabies-ChR2). By monosynapic tracing using Rabies-ChR2 from dopaminergic cells of the VTA and serotonergic cells of the DR, we were able to optogenetically stimulate these presynaptic LHb populations to directly investigate their distinct roles in shaping motivated behaviors.

Disclosures: **I. Pollak Dorocic:** None. **D. Fürth:** None. **Y. Xuan:** None. **K. Meletis:** None.

Poster

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Topic: F.03. Motivation and Emotion

Support: National Science Foundation of China Grant 91332122/31171047

Title: Different outputs of lateral hypothalamus GABAergic neurons control appetitive and consummatory behaviors

Authors: C. ZHU, *S. SONG, Y. XIONG, W. SHI;
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Abstract: The GABAergic neuron in lateral hypothalamus (LH) has been found playing an important role in feeding behavior. Activation of LH GABAergic neuron produces appetitive and consummatory behaviors, and these two behaviors are encoded in distinct neurons (Stuber ,2015). We think the two kinds of GABAergic neurons may have different inputs and outputs, especially the outputs. We first do anterograde tracing in LH in wild type (WT) and VGAT-ires-cre mice to get the projection profile. Compared with the overall neurons, GABAergic neurons sends more projection to midbrain and pons, less to cortex and spetum. By using optogenetic tools, we find that activation of GABAergic projections mainly increase feeding behavior and show a preference to high fat food than normal food. Interestingly, the behavior of these projections has a little different. Activating LH->midbrain GABAergic projections such as LH->VTA GABAergic projection increases feeding and induces unusual appetitive motor sequences such as licking and gnawing the floor or empty space as shown in another paper(Edward H.Nieh,2015), while activating LH->pons GABAergic projections shows a mixed behavior including seeking and feeding. At the beginning of stimulation, the mice show more seeking behavior than feeding behavior, as the experiment processing, seeking behavior component decreases and feeding behavior component increases.

Disclosures: **C. Zhu:** None. **S. Song:** None. **Y. Xiong:** None. **W. Shi:** None.

Poster

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FCT PhD grant SFRH/BD/89936/2012

Title: Activation of D2-expressing neurons in the nucleus accumbens enhances motivation

Authors: *C. SOARES-CUNHA[1,2], B. COIMBRA[1,2], A. DAVID-PEREIRA[1,2], S. BORGES[1,2], L. PINTO[1,2], A. J. RODRIGUES[1,2], N. SOUSA[1];
[1]Life and Hlth. Sci. Res. Inst. (ICVS), Braga, Portugal; [2]ICVS/3B's - PT Government Associate Lab., Braga/Guimarães, Portugal

Abstract: Natural rewards, such as food or sex, exhibit reinforcing properties by activating the mesolimbic system, which comprises dopaminergic projections arising from the ventral tegmental area to the medium spiny neurons (MSNs) of the nucleus accumbens (NAc). These GABAergic MSNs comprise up to 95% of all NAc neurons and are typically segregated into two distinct subtypes - those expressing dopamine D1-type receptors (direct pathway) and those expressing dopamine D2-type receptors (indirect pathway). Whereas D1-MSN activation is canonically related to positive valence and induces persistent reinforcement, D2-MSN signalling is thought to mediate aversion. However, this functional/behavioural bias of both types of MSNs has been questioned by some pharmacological and genetic studies. In this perspective, we decided to use novel optogenetic tools to selectively stimulate accumbal D2 neurons and evaluate its modulatory effects in different motivation-related behaviours. In the present report, we first show that the pattern of activation of NAc neurons predicts motivational drive. Also, we found a positive correlation between the number of activated D2-expressing neurons and behavioural performance in a motivation-dependent task. We subsequently show that optogenetic modulation of D2 neurons enhances motivation in different behavioural paradigms and is able to induce behavioral conditioning. To complement these findings, we show that specific D2-neuronal activation in the NAc normalized motivational deficits in an animal model of stress-induced anhedonia. Altogether these results demonstrate that activation of D2 neurons in the NAc is necessary to modulate motivated behaviours.

Disclosures: C. Soares-Cunha: None. **B. Coimbra:** None. **A. David-Pereira:** None. **S. Borges:** None. **L. Pinto:** None. **A.J. Rodrigues:** None. **N. Sousa:** None.

Poster

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Uppsala University

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Title: A mesoaccumbal glutamatergic population that induces aversion when stimulated optogenetically

Authors: *S. PUPE, J. PEDERSEN, T. VIERECKEL, C. J. A. SMITH-ANTILLA, M. LAGERSTRÖM, Å. WALLÉN-MACKENZIE;
Uppsala Univ., Uppsala, Sweden

Abstract: The ventral tegmental area (VTA) is traditionally recognized as a hub for processing reward-related stimuli, particularly via its projections to the nucleus accumbens (NAcc). In the past few years, a more detailed picture of the mechanisms through which the VTA mediates reward and aversion has emerged, mainly through an understanding of how the different cell types in this structure and their projections interact to produce behavior. In this work, we characterize the anatomy and function of a population of cells defined by the expression of a specific promoter (further referred as VTA1), located mostly in the anterior part of the VTA. Through *in situ* hybridization, we have verified that a sizable majority of these cells express the vesicular glutamate transporter type 2 (VGLUT2), a characteristic that suggests they release glutamate. After injection of Channelrhodopsin-2 in VTA1-Cre mice, they preferred to avoid the optogenetic stimulation of VTA1+ cells in the VTA in a real-time place preference test. This aversive response was even stronger when the stimulation was directed towards the NAcc medial shell, a target of dense projections from the VTA1 population. We were able to establish that approximately half of postsynaptic cells in the NAcc medial shell display EPSPs when these projections are stimulated optogenetically, and that these EPSPs can be blocked by AMPA receptors, suggesting glutamate is being released in these synapses. To establish whether glutamate was the neurotransmitter mediating the behavioral response that we saw, we crossed VTA1-Cre mice with a Vglut2-Lox line, generating conditional knockouts in which glutamate was not released by these cells anymore. When the real-time place preference test was performed again, no aversion was found either by stimulating in the VTA or in the NAcc. In conclusion, we believe that the neuronal population characterized by expression of VTA1 in the midbrain is mostly glutamatergic, and the excitation produced in the NAcc by its stimulation induces aversion.

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Poster

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Topic: F.03. Motivation and Emotion

Support: This work is supported by NIDA-IRP.

Title: Selective activation of glutamatergic inputs from the pedunculopontine tegmental nucleus to the ventral tegmental area is reinforcing

Authors: *H.-L. WANG[1], A. CHAKRABORTI[1], S. ZHANG[1], J. QI[1], S. STEIDL[2], M. MORALES[1];
[1]IRP/NIDA/NIH, Baltimore, MD; [2]Dept. of Psychology, Loyola Univ. Chicago, Chicago, IL

Abstract: The pedunculopontine tegmental nucleus (PPTg) has been implicated in reward function. The PPTg is composed of cholinergic (expressing choline acetyltransferase; ChAT), GABAergic (expressing glutamic acid decarboxylase; GAD), and glutamatergic (expressing vesicular glutamate transporter 2; VGluT2) neurons (Wang & Morales, 2009). While these neurons are know to provide inputs to the ventral tegmental area (VTA), the relative proportions with which they innervate the VTA are not known. To identify and quantify PPTg neurons projecting to the VTA, we injected the retrograde tracer Fluoro-Gold (FG) into VTA, and phenotyped FG-labeled PPTg neurons by *in situ* hybridization. We found that among PPTg FG-neurons nearly 67% expressed VGluT2 mRNA, 17% expressed ChAT mRNA, and nearly 16% expressed GADs mRNA. Thus the major projection from the PPTg to the VTA is glutamatergic, with minor projections arising from cholinergic or GABAergic neurons. To determine PPTg glutamatergic postsynaptic targets in the VTA, PPTg glutamate neurons were selectively tagged with channelrhodopsin 2 (ChR2) tethered to mCherry in VGluT2::Cre mice. Axon terminals from tagged PPTg-VGluT2 neurons established asymmetric synapses mainly on dopamine neurons. We next tested whether optical stimulation of PPTg glutamate inputs to the VTA established instrumental responding. In these behavioral studies, PPTg VGluT2 neurons were transfected with either yellow fluorescent protein (VGluT2-eYFP) alone or eYFP tethered to ChR2 (VGluT2-ChR2-eYFP). Mice were implanted with optic probes aimed at the VTA and were allowed to earn VTA optical stimulation by rotating one of two response wheels. VGluT2-ChR2-eYFP mice, but not VGluT2-eYFP mice, rotated the reinforced (‘active’) wheel

significantly more often than the non-reinforced ('inactive') wheel. To confirm that wheel-turning was goal-directed, we switched the contingencies between the wheels for 4 days of reversal testing following 8 days of training. VGluT2-ChR2-eYFP mice switched to the newly reinforced wheel during the first reversal session and continued responding on this wheel for three subsequent reversal testing sessions. Together, the data suggest that (1) the majority of inputs from the PPTg to the VTA are glutamatergic; (2) within the VTA, the PPTg provides glutamatergic inputs mainly to dopamine neurons; (3) VTA selective excitation of PPTg glutamatergic inputs elicits reliable intracranial self-stimulation in VGluT2::Cre mice.

Disclosures: H. Wang: None. **A. Chakraborti:** None. **S. Zhang:** None. **J. Qi:** None. **S. Steidl:** None. **M. Morales:** None.

Poster

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Topic: F.03. Motivation and Emotion

Support: NIDA-IRP

Title: Monosynatic inputs to ventral tegmental area glutamate neurons

Authors: *C. MEJIAS-APONTE[1], B. B. GARCIA IGLESIAS[2], D. J. BARKER[2], S. ZHANG[2], M. MORALES[2];
[1]Neuronal Networks Section, INRB, NIDA-IRP, NIH, Baltimore, MD; [2]Neuronal Networks Section, Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Glutamate neurons are one of the three major cell types of the ventral tegmental area (VTA). These neurons express vesicular glutamate transporter 2 (VGluT2), a marker of glutamate neurotransmitting neurons. Like VTA dopamine and GABA, glutamate neurons send forebrain afferents to brain networks involved in psychiatry disorders including schizophrenia and addiction. To better understand the function of VTA glutamate neurons, we set to investigate their afferents. Using a transgenic mouse line that expresses Cre under the regulation of the VGluT2 promoter, we targeted VGluT2-expressing VTA neurons for monosynaptic tract-tracing using the modified pseudorabies technique. Specifically, VGluT2::Cre mice were injected with adenoviral vectors into the VTA to selectively express an avian cognate receptor, TVA, a mammalian rabies glycoprotein (RG), and the fluorescent reporter mCherry in VTA VGluT2 neurons. Three weeks after, a rabies vector modified with an avian glycoprotein and the

fluorescent reporter green fluorescent protein was injected into the VTA. The initial "starter" neurons from which afferents were identified from were delineated by co-expression of green fluorescent protein and mCherry. The neurons monosynaptically projecting to VTA VGluT2 neurons were delineated by expression of green fluorescent protein alone. Approximately one week after the rabies vector was delivered, brains were collected. Retrogradely-labeled neurons were mapped throughout the brain. Because of the ubiquitous expression of VGluT2 neurons in area surrounding the VTA, control injections were also made in a number of proximal regions including the suprammamillary, red nucleus, and interpeducular nucleus. Ongoing experiments are aimed to verify major inputs to VGluT2-VTA neurons using anterograde tracing.

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Poster

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Topic: F.03. Motivation and Emotion

Support: Intramural Research Program at NIDA/NIH

Title: Brain mapping of neurons with a dual glutamatergic-GABAergic phenotype

Authors: *D. H. ROOT, H.-L. WANG, M. MORALES;
Neuronal Networks Section, Natl. Inst. on Drug Abuse, Baltimore, MD

Abstract: Glutamate is both a metabolic amino acid and an excitatory neurotransmitter. As a metabolic amino acid, glutamate is a substrate for protein synthesis and a substrate for the enzyme glutamic acid decarboxylase (GAD) to produce the inhibitory neurotransmitter GABA. As a neurotransmitter, glutamate is accumulated in synaptic vesicles by one of three known vesicular glutamate transporters (VGluT1, 2, and 3), while GABA is accumulated in synaptic vesicles by the vesicular GABA transporter (VGaT). The VGluTs and VGaT are incorporated into the membranes of synaptic vesicles that get concentrated in axon terminals. Upon neuronal depolarization and presynaptic calcium entry, each of these vesicles release either glutamate or GABA. Accumulating evidence indicates that VGluTs are in different neurons from those containing GAD and VGaT. Thus glutamate is largely used as signaling molecule by a set of neurons different from other neurons that use GABA as signaling molecule. However, we had identified in the ventral tegmental area a group of neurons that co-express transcripts encoding

VGluT2 and GAD. These neurons target the lateral habenula and co-release from the same axon terminal glutamate and GABA (Root et al., 2014; Nat Neurosci). In order to determine if $VGluT2^+$ GAD^+ neurons exist in other brain regions, we used a combination of double *in situ* hybridization to map neurons co-expressing VGluT2 mRNA and GAD mRNA across the rat brain. Major populations of $VGluT2^+$ GAD^+ neurons were observed in a select group of subcortical regions: the entopeduncular nucleus, lateral subregion of the supramammillary nucleus, anterior and medial subregions of the ventral tegmental area, and the posterodorsal tegmental nucleus. As all four regions in which $VGluT2^+$ GAD^+ neurons were identified have well-established projections to limbic structures, we hypothesize that $VGluT2^+$ GAD^+ neurons play unique roles in learning, memory, motivation, and emotionality. To test this hypothesis we are currently mapping the distinct circuits involving $VGluT2^+$ GAD^+ neurons. This research was supported by the intramural research program at NIDA/NIH.

Disclosures: D.H. Root: None. **H. Wang:** None. **M. Morales:** None.

Poster

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Topic: F.03. Motivation and Emotion

Support: Intramural Research Program of the National Institute on Drug Abuse

Title: The lateral habenula receives an unexpected glutamatergic input from the lateral preoptic area

Authors: *D. J. BARKER[1], D. H. ROOT[2], H.-L. WANG[2], S. ZHANG[2], M. MORALES[2]; [1]Natl. Inst. On Drug Abuse- Intramural Resea, Baltimore, MD; [2]Neuronal Networks Section, Natl. Inst. on Drug Abuse, Intramural Res. Program, Baltimore, MD

Abstract: The Lateral Habenula (LHb) has been identified as a brain region that plays important roles in drug abuse, psychiatric illnesses and motivated behavior. Convergent evidence has established that the LHb receives a major input from the Lateral Preoptic Area (LPO). Although the nature of this LPO-LHb pathway hasn't bee determined, it has been prosed to be inhibitory, presumably from LPO GABAergic neurons. Here, we characterized the anatomical and functional network between the LPO and the LHb. To identify specific LPO neurons targeting the LHb, the retrograde tracer fluorogold was injected into the LHb (1% via iontophoresis). Next, we established the phenotype of the fluorogold-tagged neurons by *in situ* hybridization

detection of transcripts encoding either glutamic acid decarboxylase 65/67 mRNA (GAD, a marker of GABAergic neurons) or vesicular glutamate transporter 2 mRNA (VGluT2, a marker of glutamate neurons). Surprisingly, we found that within the total population of fluorogold-positive neurons only 15.9 ± 3.2% expressed GAD mRNA, and as many as 74.7 ± 3.2% expressed VGluT2 mRNA. These neuroanatomical findings indicate that the major projection from the LPO to the LHb is from excitatory glutamatergic neurons rather that from inhibitory GABAergic neurons, as has been previously proposed. Based on our current understanding of the habenula, this suggests that the LPO-LHb glutamatergic pathway may be important for numerous psychopathologies including depression or the aversive effects of psychostimulants. Future work will focus on the participation of the LPO-LHb glutamatergic pathway in ongoing behavior in order to specifically investigate its participation in psychiatric illness.

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Poster

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Support: This work is supported by NIDA-IRP.

Title: Feeding behavior and reward are differentially induced by optogenetically activating GABAergic lateral hypothalamic projections to VTA at different stimulation frequencies

Authors: *M. F. BARBANO[1], H. WANG[2], R. WISE[2], M. MORALES[2];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Neuronal networks section, NIDA/NIH, Baltimore, MD

Abstract: The lateral hypothalamus (LH) is a heterogeneous brain structure that has been classically involved in feeding, motivation and reward. Optogenetic approaches have recently confirmed that GABAergic LH neurons induce feeding and reward. It has also been shown that GABAergic projections from the LH to the ventral tegmental area (VTA) modulate feeding and compulsive sucrose seeking. However, it is still unclear if the same population of GABAergic lateral hypothalamic neurons that projects to the VTA promotes both feeding and reward. In the present study, we addressed this question by using a combination of optogenetic, behavioral, and pharmacological techniques in transgenic male mice expressing Cre recombinase under the regulation of the vesicular GABA transporter (VGaT::Cre mice). We found that VTA

photoactivation of GABAergic LH projections using low frequencies (5 Hz but not 40 Hz) promoted feeding in food sated mice. This effect was decreased by the intra-VTA administration of a mix of GABA A and B antagonists. Conversely, photostimulation of the same pathway was highly rewarding and reinforced instrumental behavior when high frequencies were used (40 but not 5Hz). The best operant performance was achieved using high frequencies of stimulation (40 Hz). The motivated operant responses were also reduced by the administration of GABA antagonists. To further characterize the reinforcing properties of low and high frequencies of stimulation on reward, we conducted a place conditioning study. Different groups of mice received continuous photostimulation with frequencies either low (5 Hz) or high (40 Hz) after entering a light-paired chamber on a three chamber apparatus. Only mice conditioned with the high frequency showed a significant preference for the light-paired chamber during training and also during subsequent testing, when the light was no longer available. These and similar findings confirm that activation of GABA fibers originating from the lateral hypothalamus and projecting to the ventral tegmental area can contribute to the rewarding and feeding-inducing effects long established by electrical stimulation studies. It is unclear if the differential effectiveness of low and high frequency stimulation reflects the activation of different subsets of GABA neurons or difference levels of responses by the same group of GABA neurons.

Disclosures: **M.F. Barbano:** None. **H. Wang:** None. **R. Wise:** None. **M. Morales:** None.

Poster

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Topic: F.03. Motivation and Emotion

Support: NIH-NIDA-IRP

Title: Glutamatergic neurons from the ventral tegmental area establish multiple synapses on single parvalbumin-GABAergic interneurons in the nucleus accumbens

Authors: ***S. ZHANG**, J. QI, M. MORALES;
Natl. Inst. of Health, Natl. Inst. on Drug Abuse, IRP, Baltimore, MD

Abstract: The ventral tegmental area (VTA) is thought to play a role in goal directed behavior and in the reward processing of natural rewards and on several drugs of abuse (Schultz, 2002; Wise, 2004). Two populations of VTA neurons (dopaminergic neurons and GABAergic neurons) have been extensively characterized. However, recent findings indicate that the VTA has neurons

that express the vesicular glutamate transporter 2 (VGluT2). VGluT2 is integrated into membranes of synaptic vesicles for the accumulation of glutamate. The VTA-VGluT2 neurons are diverse in their biochemical composition and connectivity (Morales and Root, 2014). We recently found that nucleus accumbens (nAcc) optical stimulation of fibers from VTA-VGluT2 neurons evokes conditioned place aversion mediated by local release of GABA, which is accompanied by expression of c-Fos in parvalbumin-GABAergic interneurons (Qi et al., 2015 SfN). To determine the synaptic connectivity established by VTA-VGluT2 neurons in the nAcc, we used a combination of cell specific viral vector tracing and immunoelectron microscopy. In these studies, axons from VTA glutamatergic neurons were tagged by the *in vivo* expression of channelrhodopsin-2 [(ChR2) tethered to mCherry] in the VTA-VGluT2 neurons of VGluT2::Cre mice. By double immunolabeling and electron microscopy, we detected in the nAcc medial shell axon terminals containing immunoreactivity (IR) for both VGluT2 and mCherry, indicating that these VGluT2-IR/mCherry-IR-terminals were originated from VTA glutamatergic neurons. Further analysis of these VGluT2-IR/mCherry-IR-terminals showed that they made asymmetric (excitatory type) synapses on dendrites. Next, by triple immunoelectron microscopy, we found the VTA VGluT2 neurons established multiple synapses on a single parvalbumin-GABAergic interneuron. The mesoaccumbens glutamatergic pathway shown here to form multiple asymmetric synapses on parvalbumin-GABAergic interneuron is the first anatomically identified glutamatergic pathway to nAcc GABAergic interneurons.

Disclosures: **S. Zhang:** None. **J. Qi:** None. **M. Morales:** None.

Poster

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Topic: F.03. Motivation and Emotion

Support: NIH/NIDA-IRP

Title: Glutamatergic inputs from the ventral tegmental area to nucleus accumbens drive aversion by acting on GABAergic interneurons

Authors: ***J. QI**, H.-L. WANG, S. ZHANG, D. J. BARKER, M. MORALES;
Natl. Inst. On Drug Abuse, Baltimore, MD

Abstract: The ventral tegmental area (VTA) is best known by its dopamine neurons, some of which project to the nucleus accumbens (nAcc). However, the VTA also has glutamatergic

neurons that innervate the nAcc. The role of this mesoaccumbens glutamatergic pathway remains unknown. Here, we report that within the nAcc, fibers from mesoaccumbens-glutamate neurons, which mostly innervate the nAcc shell, form local asymmetric synapses (Zhang et al., 2015 SfN). Photoactivation of mesoaccumbens glutamatergic fibers promotes conditioned place aversion, and establishes escape-avoidance responding in both a negative-reinforcement task and a positive-reinforcement task. Although the mesoaccumbens glutamatergic fibers lack GABAergic markers, the aversion evoked by these fibers depends on glutamate and GABA receptors, but not on dopamine receptors. The mesoaccumbens glutamatergic fibers make multiple asymmetric synapses on parvalbumin interneurons in the nAcc, and photoactivation of these mesoaccumbens glutamatergic fibers elicits activation of parvalbumin interneurons. Moreover, photoactivation of nAcc parvalbumin interneurons also promotes aversion. We conclude that mesoaccumbens glutamatergic neurons play a role in controlling inhibitory neurotransmission within the nAcc shell. The mesoaccumbens glutamatergic pathway is the first glutamatergic input to nAcc shown to mediate aversion, rather than reward.

Disclosures: **J. Qi:** None. **H. Wang:** None. **S. Zhang:** None. **D.J. Barker:** None. **M. Morales:** None.

Poster

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Topic: F.03. Motivation and Emotion

Title: Connectivity of neural microcircuitry in frontal cortex revealed by large-scale network imaging

Authors: *J. T. TRACHTENBERG, P. GARCIA-JUNCO CLEMENTE, D. RINGACH, E. TRING;
UCLA, Los Angeles, CA

Abstract: We present a novel approach to microcircuit analysis based on resonant-scanning 2-photon imaging of large populations of identified cortical neurons in frontal cortex of behaving mice. Gcamp6-slow was used to image inhibitory neurons, using cell type-specific cre-driver lines that also expressed a red-fluorescent protein, and excitatory neurons were imaged, simultaneously, using Gcamp6-fast. Interneurons expressing vasointestinal peptide (VIP) are strongly activated during alertness, as measured by monitoring pupil diameter and running, whereas the activity of interneurons expressing somatostatin (SOM) was strongly suppressed.

Notably, fast spiking, parvalbuming (PV)-expressing interneurons and excitatory pyramidal (PYR) neurons responded heterogeneously to alertness, with half the population strongly activated in alert states and the other half strongly suppressed. When mice stopped running, these populations reversed their activities, with the formerly suppressed neurons now strongly active and the formerly active now strongly suppressed. Hereafter we refer to these cells as PV-up and PV-down, and PYR-up and PYR-down. Correlation coefficients across cell groups and across mice identify a novel and very specific microcircuit in which VIP interneurons and PYR-up neurons receive a common feedback, neuromodulatory input, possibly from adrenergic neurons in the locus coerruleus. Once activated in the alert state, VIP neurons strongly suppress PYR-down neurons. Thus, VIP interneurons appear to target a specific population of PYR neurons. In a second microcircuit revealed by our approach, presumptive thalamic input drives the activity of PV-down, PYR-down, and SOM interneurons, and not other cell types. These findings reveal a novel and specific microcircuitry in frontal cortex that is readily testable. Significantly, we find that cell populations once thought to be fairly homogeneous are in fact bistable and that this bistability underlies brain states associated with alertness and quiescence.

Disclosures: **J.T. Trachtenberg:** None. **P. Garcia-Junco Clemente:** None. **D. Ringach:** None. **E. Tring:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.01/CC58

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: DFG Grant SFB TRR 58

Title: Epigenetics of social anxiety disorder: Oxytocin receptor gene (OXTR) hypomethylation as a risk marker?

Authors: *C. ZIEGLER[1], I. LAEGER[2], S. STEVENS[3], K.-P. LESCH[4], V. AROLT[2], A. GERLACH[3], J. DECKERT[1], P. ZWANZGER[2], K. DOMSCHKE[1];
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Abstract: Social anxiety disorder (SAD) is an anxiety disorder affecting 6.8% of the US population. Oxytocin (OXT) is a neuropeptide produced in the hypothalamic paraventricular and supraoptic nucleus. It binds to a G protein-coupled receptor (OXTR) widely expressed in the central nervous system. The oxytocin peptide has been suggested as a promising anxiolytic pharmacotherapeutic agent in disorders related to social dysfunction. The oxytocin receptor gene (OXTR) located on chromosome 3p25.3 has been implicated in social cognition and behavior. The A allele of the 6930G>A (rs53576) variant was associated with non-beneficial social traits in humans. Recently, epigenetic modifications have been suggested as dynamic regulatory mechanisms of gene expression. The present study for the first time investigates the role of OXTR methylation in SAD on a categorical as well as a dimensional phenotype level. One-hundred and ten patients with SAD (f=76; age: 33.0+1.0) and 110 age- and sex-matched healthy controls were analyzed for OXTR methylation at 12 CpG sites located in the protein-coding region of the gene by direct sequencing of sodium bisulfite converted DNA extracted from whole blood. Dimensional measures of social anxiety severity were ascertained in both patients and controls using the Social Phobia Scale (SPS) and the Social Interaction Anxiety Scale (SIAS). Furthermore, patients and controls were genotyped for the 6930G>A (rs53576) variant located in the third intron of the OXTR gene. Patients with social anxiety disorder showed significantly decreased overall OXTR methylation as compared to healthy controls, particularly conferred by methylation at a single CpG dinucleotide CpG 3 ($F=8.111$; $p<0.001$). Furthermore, methylation at this CpG site negatively correlated with SPS scores ($r=-0.393$; $p<0.001$) and SIAS scores ($r=-0.399$; $p<0.001$) across patients and controls. A-allele carriers of the 6930G>A variant showed significant decreased overall OXTR methylation across patients and controls ($F=5.045$; $p=0.007$). The present results provide multi-level evidence for a role of OXTR hypomethylation in social anxiety disorder. A hypomethylation of the OXTR gene potentially leads to an up-regulation of the gene expression which could serve as a compensatory mechanism for lower overall oxytocin levels found in patients with social anxiety disorder. Anyway, given robust replication, OXTR hypomethylation could serve as a peripheral biomarker of disease risk and/or severity and might finally allow for indicated preventive interventions as well as more personalized treatment options targeting the oxytocin system.

Disclosures: **C. Ziegler:** None. **I. Laeger:** None. **S. Stevens:** None. **K. Lesch:** None. **V. Arolt:** None. **A. Gerlach:** None. **J. Deckert:** None. **P. Zwanzger:** None. **K. Domschke:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.02/CC59

Topic: F.03. Motivation and Emotion

Support: Canadian Institutes of Health Research Grant MOP89758

Title: Effect of a single episode of footshock on anxiety and neuropeptide precursors in the striatum and extended amygdala

Authors: *H. WANG[1], S. LI[1], G. J. KIROUAC[1,2];
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Abstract: Corticotropin releasing factor (CRF) and dynorphin are neuropeptides that have been associated with negative emotional states. Experimental evidence indicates that dynorphin neurons located in the nucleus accumbens (NAc) and CRF neurons in the bed nucleus of the stria terminalis (BST) and the amygdala mediate the behavioral effects produced 24-48 hrs after exposure to a stressful episode. The present study was done to evaluate if changes in the levels of the mRNA for these peptides in the striatum, BST, and amygdala were associated with the long-lasting anxiety induced in a subset of rats exposed to moderately intense footshocks. On day 1, shocked rats were exposed to footshocks (5 × 2 s of 1.5 mA presented randomly over 3 min), whereas nonshocked (NS) rats were placed in the shock chamber for 5 min. On day 2, rats were tested in a novel chamber and according to the amount of time spent immobile, shocked rats were grouped as high responders (HR; immobility > 60%) or low responders (LR; immobility < 40%). On day 3, fear to the shock context was assessed by measuring immobility to the shock chamber for 5 min. On days 10 & 11, the elevated T-maze (ETM) was used to assess avoidance (a measure of anxiety) and escape (a measure of helplessness). On day 14, the rats were anesthetized and the amygdala, BST, NAc and caudate putamen were removed for analysis using real-time RT-PCR. HR displayed long-lasting anxiety in the elevated T-maze whereas LR had low levels of anxiety similar to NS rats. An enhanced level of CRF mRNA was detected in the amygdala of the HR compared to LR and NS rats. In contrast, CRF, prodynorphin and proenkephalin mRNA levels in the striatum, BST and amygdala were not different between HR, LR and NS rats. This study provides evidence that CRF neurons in the amygdala play a role in the long-lasting anxiety produced in a subset of rats exposed to footshocks.

Disclosures: H. Wang: None. **S. Li:** None. **G.J. Kirouac:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.03/CC60

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: entre Hombres y Mujeres program (INMUJERES-SHCP-CAM.DIPUTADOS 2013

Conacyt project #CB2010/155255

Title: Effect of progesterone withdrawal on experimental anxiety and hypothalamus - pituitary-adrenal axis in Wistar and Wistar Kyoto in intact female rats

Authors: *D. M. ISLAS[1], P. DE GORTARI[1], N. VEGA-RIVERA[1], C. LÓPEZ-RUBALCAVA[2], G. UGALDE-FUENTES[1], E. ESTRADA-CAMARENA[1];
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Abstract: Women with Premenstrual Dysphoric Disorder (PMDD) showed high levels of anxiety and a blunted response to stress of serum corticosterone (CORT) and Allopregnanole (ALLO) levels during the luteal phase of the menstrual cycle (Girdler et al., 2007). Here, Wistar Kyoto (WKY) rats were used to evaluate the effect of progesterone withdrawal (PW), as an animal model of PMDD, on the Hypothalamus-Pituitary-Adrenal axis (HPA) response through CRH, GR mRNA expression in PVN and Hippocampus as well as CORT serum levels. Also, the mRNA expression of the 5α-reductase type 2 (5αRED2) enzyme in hippocampus and PVN and ALLO serum levels was determined. WKY strain present HPA axis hyper-reactivity toward stressful stimuli in relation to Wistar (W) strain and show high levels of anxiety- and depression-like behaviors, two traits of PMDD. Intact female Wistar (as a control strain) and WKY rats (250-300g) were randomly assigned to independent groups: one treated with vehicle (corn-oil) and other with progesterone (0.5 mg/kg, s.c., daily for 5 days) per strain. Twenty-four hours after a last administration of hormonal treatment, animals were tested in the Burying Behavior Test (BBT) and euthanized by decapitation 60 min later. Brain and blood were immediately collected and stored at -70 ◦C for posterior analysis of CRH, GR, 5αRED2 mRNA expression by RT-PCR and CORT and ALLO by commercial ELISA kits. Results showed that anxiety like behavior was augmented in both strains as a consequence of PW. In vehicle treated groups higher levels of serum CORT, CRH and GR mRNA expression and lower levels of ALLO were observed in WKY respect to W ($p<0.05$); no differences in 5αRED2 expression were noted. In response to PW, hippocampal CRH expression was augmented in WKY when compare against its proper control ($p<0.05$) and no changes were observed in GR and 5αRED2 expression. On the contrary, in PVN of WKY both CRH and GR expression decrease in PW ($p<0.05$) while no changes in W were observed. 5αRED2 mRNA enzyme expression was increased in W but not in WKY ($p<0.05$). Finally CORT and ALLO levels were similar to the vehicle control group in both strains, suggesting a no response to PW. The fact that 5αRED2 mRNA expression and CORT and ALLO did not change in response to PW in WKY rats suggests that this strain might be useful to establish neurobiological correlates that contribute to PMDD study.

Disclosures: **D.M. Islas:** None. **P. De Gortari:** None. **N. Vega-Rivera:** None. **C. López-Rubalcava:** None. **G. Ugalde-Fuentes:** None. **E. Estrada-Camarena:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.04/CC61

Topic: F.03. Motivation and Emotion

Support: DGAPA Grant IN 203111

DGAPA Grant IN 204314

Title: Role of arginine vasopressin on the amygdaloid modulation of fear and anxiety in the rat

Authors: *O. R. HERNANDEZ PEREZ[1], E. PALOMARES[2], M. CRESPO RAMIREZ[2], M. PÉREZ DE LA MORA[2], K. FUXE[3];
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Abstract: The amygdala plays a central role in fear and anxiety. Vasopressinergic fibers project from the hypothalamus and strongly innervate medial amygdala (MeA) and bed nucleus of the stria terminalis (BNST). Three different receptors have been so far identified for vasopressin effects (V1a, V1b and V2 receptors). V1b receptor has been identified within the central amygdaloid nucleus and its participation in the amygdaloid modulation of anxiety has been suggested. Behaviorally, the intra-amygdaloid infusion of arginine vasopressin agonists and antagonists elicits anxiogenic and anxiolytic effects respectively on conditioned models of anxiety. However, the role of arginine vasopressin in unconditioned anxiety is less known and even contradictory. The aim of this study was to evaluate the behavior of rats in the elevated plus-maze and the shock-probe burying test following vasopressin administration (1 an 10 ng/side) within the central amygdaloid nucleus. The effects of the simultaneous administration of arginine vasopressin (1 ng/side) and SSR149415 (1 and 10 ng/side), a specific V1b vassopresin receptor antagonist, were also tested in the same paradigms and dark light box. The results showed that the bilateral microinjection of arginine vasopressin at lower (1ng /side) but not at higher (10 ng/side) doses significantly increased the time spent by the rats in the open arms of the elevated plus-maze as compared with their saline-treated controls. No effects of this treatment were observed on the total number of entries into open + closed arms of the maze. In

contrast, the infusion of arginine vasopressin (1ng/side) increased the burying behavior in the shock-probe burying test. Interestingly, this last behavior was not observed when SSR149415 was administered simultaneously with vasopressin. Our results suggest, that the bilateral administration of arginine vasopressin is dependent effects of the test used to assess anxiety and seems to have effects on higher aversion paradigms while those that are less aversive its after effects seem to be low or absence of such.

Disclosures: O.R. Hernandez Perez: None. **E. Palomares:** None. **M. Crespo Ramirez:** None. **M. Pérez de la Mora:** None. **K. Fuxe:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.05/CC62

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Cannabinoid receptor 2 activation and anxiety after repeated social defeat stress

Authors: *H. J. STRATTON[1], D. ALLEN[3], J. WU[2];
[1]Neurol. Res., [2]Barrow Neurolog. Inst., Phoenix, AZ; [3]Arizona State Univ., Tempe, AZ

Abstract: The United States population has a 12-month incidence for anxiety-related disorders of 18.1% and affects more than 40 million individuals nationwide. Components of the behavioral response to stressful stimuli are mediated by G-Protein Coupled Receptors (GPCR's) of the endogenous cannabinoid system (ECS). These receptors have been demonstrated to act as primary regulators of behavioral and cellular alterations following exposure to stressful stimuli. Recent evidence has localized cannabinoid receptor 2 (CB2) to the CNS where it has been found on neurons and glial cells. This receptor is of particular interest because it has been shown to alter the activity of DA neurons within the VTA, which is a primary regulatory nucleus in the expression of anxiety behavior (Figure 1). Increased DA neuron firing originating in the VTA is strongly associated with exposure to social defeat stress and preliminary data shows mice lacking the CB2 receptor demonstrate an enhanced to response to social defeat (Figure 2). This effect is potentially driven by CB2 activation altering DA neuron output, which indicates a potential role for this receptor in modulating VTA DA neuronal output to reduce expression of pathological levels of anxiety. Behavioral evidence suggests CB2 over-expression produces an anxiety-resistant phenotype and that application of CB2 specific agonist JWH133 results in reduced expression of anxiety behavior in non-stressed mice. Additionally, data obtained from dissociated single DA neurons from the VTA demonstrated that application of the JWH-133

decreased the firing rate of spontaneous action potentials from these neurons. This study sought to determine the effects of CB2 activation on the expression of anxiety behavior as well as the activity of VTA DA neurons in socially stressed mice. The open field test was used to determine the effects of systemic application of JWH133 on the expression of anxiety behavior in C57BL/6J mice following repeated submaximal social defeat stress. Multi-electrode field recording of VTA slices in the same mice were employed to determine the effects of JWH133 on this social defeat stress-induced altered activity. CB2-/- mice underwent the same experimental conditions with a saline vehicle to compare the expression of anxiety behavior and alteration in VTA DA firing to wild type littermates following social stress. Results indicate a possible role for CB2 receptor activation in the reduction of anxiety behavior and the restoration of normal firing patterns in the VTA following social stress.

Disclosures: **H.J. Stratton:** None. **D. Allen:** None. **J. Wu:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.06/CC63

Topic: F.03. Motivation and Emotion

Title: Sex difference in anxiety-like effects of the THC agonist CP55,940

Authors: *H. T. FRENCH[1], A. KLAMBATSEN[2], S. JENAB[1], V. QUINONES-JENAB[2]; [2]Psychology, [1]Hunter Col., New York, NY

Abstract: Aim: Sexual dimorphism exists at different levels of the cannabinoid system and THC induced responses, including receptor distribution, metabolic processing of THC, and analgesic responses. Anxiety responses in both human and animal males are dose dependent: low acute doses of cannabinoids are anxiolytic while high and/or chronic doses are anxiogenic. In this study we aimed to examine if the biphasic behavioral effects of cannabinoids that have been demonstrated in males are also present in females. Methods: Male and female Wistar rats (8 weeks old) received 0, 0.001, 0.01, 0.075 or 0.125 mg/kg i.p. of the THC agonist CP55,940_n=10-11 per group. Thirty minutes later, animals were placed in the elevated plus maze (EPM) for 10 minutes, and their behavior analyzed by Med Associates tracking software. Results: A significant main effect of CP55,940 doses was observed [$F(4, 92) = 6.863$, $p < 0.01$]; 0.075 mg/kg showed a significant reduction in percent time in open arms compared to vehicle ($p = 0.05$). Furthermore, 0.001mg/kg showed significantly more time in open arms than: 0.01 ($p = 0.045$), 0.075 ($p < 0.01$) and 0.125 ($p < 0.01$). Conclusion: Sex differences were observed in the

effect of CP55,940 on anxiogenic and anxiolytic responses. Although males showed biphasic dose dependent responses to this THC agonist, female rats showed only an anxiogenic response to CP55,940. Our study is in agreement with previous studies suggesting sex-dependent behavioral effects of cannabinoids. Further research is needed to understand the underlying mechanisms responsible for these differences.

Disclosures: H.T. French: None. **A. Klambatsen:** None. **S. Jenab:** None. **V. Quinones-Jenab:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.07/CC64

Topic: A.09. Adolescent Development

Support: NIH R01MH091844

NIH RO1 MH91427

Spanish Ministry of Science postdoctoral fellowship

Title: Loss of forebrain 5-HT1A receptors results in a depression but not anxiety-like phenotype

Authors: *A. GARCIA[1], S. CANETTA[1], B. P. GUIARD[2], A. GARDIER[2], C. KELLENDONK[1], A. DRANOVSKY[1], E. D. LEONARDO[1];
[1]Integrative neuroscience, Columbia University, New York Psychiatry Inst., New York, NY;
[2]Faculté Pharmacie, Univ. Paris Sud, Chatenay-Malabry, F-92296, France., Paris, France

Abstract: Despite significant evidence linking 5-HT_{1A} receptor function to depression in humans, to date rodent models of 5-HT_{1A} function have primarily focused on anxiety. This focus may be due to the fact that early studies with the 5-HT_{1A} receptor KO mouse described a significant anxiety phenotype with no clear depressive phenotype. Interestingly, the anxiety phenotype is developmentally mediated as normal expression of 5-HT_{1A} receptors is required during the 2nd and 3rd week of life for the emergence of normal anxiety, with mice lacking functional 5-HT_{1A} receptors during this time developing pathological levels of anxiety. Recently, studies from our lab have recapitulated the anxiety phenotype of the whole-brain KO mice in 5-HT_{1A} autoreceptor KO mice. Conversely, we have previously found that whole life suppression of 5-HT_{1A} heteroreceptors affect responses to forced swim stress, without effects on anxiety-like behavior. These results coupled with the absence of a phenotype when heteroreceptors are

repressed in adult animals strongly suggested that variation in 5-HT_{1A} heteroreceptor function during development would have lasting effects on an animals baseline behavior in a manner that was distinct from that observed with autoreceptor manipulations Here, we use a genetic mouse system to independently manipulate 5-HT_{1A} heteroreceptors with temporal and spatial specificity to understand their function within raphe-forebrain circuitry. We demonstrate that mice lacking 5-HT_{1A} heteroreceptors display increased behavioral despair and anhedonia while maintaining normal anxiety levels. This behavioral phenotype was accompanied by changes in the response of prefrontal cortex neurons to stress and changes in raphe firing rates. We further found that suppression of 5-HT_{1A} heteroreceptors during adolescence was sufficient to confer these long-lasting behavioral and physiological effects. Our results demonstrate a developmentally mediated depression related phenotype that results from altered 5-HT_{1A} signaling in the forebrain. We also provide evidence to support the idea that, 5-HT_{1A} heteroreceptors in the prefrontal cortex might be responsible for this phenotype.

Disclosures: **A. Garcia:** None. **S. Canetta:** None. **B.P. Guiard:** None. **A. Gardier:** None. **C. Kellendonk:** None. **A. Dranovsky:** None. **E.D. Leonardo:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.08/CC65

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: L. reuteri decreases baseline anxiety, alters fear-related memory, and buffers stress-induced anxiety in C57/BL6 mice

Authors: *R. J. PENDRY[1], R. P. MADIGAN[2], M. D. ERIKSSON[2], J. D. WHITE[2], M. J. EIMERBRINK[2], M. J. CHUMLEY[3], G. W. BOEHM[2];
[2]Psychology, [3]Biol., [1]Texas Christian Univ., Fort Worth, TX

Abstract: This research explored how chronic ingestion of *L. reuteri* altered baseline anxiety, fear-related memory, and whether or not *L. reuteri* could protect against stress induced anxiety. All animals were weaned between 21 and 28 days of age, and were taught to self-administer 0.5 mL of a 10% sucrose MRS broth solution within approximately 20 minutes. Once trained, animals were randomly assigned to either the probiotic or vehicle treatment condition. Animals in the probiotic condition received 0.5 mL of the sucrose solution that contained the 10^9 cfu of *L. reuteri,* while vehicle-treated animals received sucrose solution only. Treatment was maintained until all animals in the cohort were at least 70 days of age, after which we began behavioral

testing. To assess anxiety behaviors, animals were first tested in an elevated zero maze, followed by two days of open field testing. Separate batches of animals were tested in both a contextual and delay conditioning paradigm. Finally, a third batch of animals was tested using a 2x2 design (treatment x stressor), during which animals from each respective treatment group was either exposed to an environmental stressor in a conditioning chamber or placed in the chamber for a comparable duration, without the stressor. To assess potential biological differences mediating behavioral changes, we evaluated peripheral corticosterone and specific neurotransmitter receptor expression in the hippocampus and amygdala. Results indicate that treatment with *L. reuteri* has the ability to decrease expression of baseline anxiety behaviors, alter fear related memory, and protect against stress-induced exaggerations of anxiety behaviors. Additionally, these behavioral changes corresponded to differential gene/protein expression. Overall, results from these studies indicate that repeated ingestion of *L. reuteri* can alter behavioral and physiological measures associated with anxiety and fear-related memory.

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Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.09/CC66

Topic: F.03. Motivation and Emotion

Title: Dissociated linkage between serotonin related gene polymorphisms, fearful voice and face processing, amygdala activity and trait anxiety: a combined fmri and erp study

Authors: *Y.-C. CHEN[1], C. CHEN[1], C.-H. HU[1], Y. CHENG[1,2];
[1]Inst. of neuroscience, Natl. Yang-Ming Univ., Taipei, Taiwan; [2]Dept. of Rehabil., Natl. Yang-Ming Univ., Yilan, Taiwan

Abstract: Serotonin transporter polymorphism (5-HTTLPR) usually links anxiety and amygdala reactivity. However, their relations seem to be mixed. Here, we enrolled 95 adults, who varied n threat sensitivity (Spielberger trait anxiety scale), and examining the amygdala reactivity in response to the conscious and nonconscious (backwardly masked) perception of fearful and angry faces and also recording the mismatch negativity (MMN) to emotionally spoken syllables *dada*. There were 12 participants (6 males) in the ll group, 48 participants (20 males) in the ls group and 35 participants (23 males) in the ss group. When the fearful MMN were treated as a latent variable, genotype was treated as independent variable, and errors were assumed to be

uncorrelated, we performed path analysis to test whether the influence of the 5-HTTLPR polymorphism on trait anxiety was dependent on its influence on the amygdala, and to find the best-fitting model from three possible candidates: (1) TPH23 amygdala 3 CGI-I; (2) TPH2 3 CGI-I 3 amygdala; (3) TPH23 amygdala, TPH2 3 CGI-I (Figure 1).

Disclosures: **Y. Chen:** None. **C. Chen:** None. **C. Hu:** None. **Y. Cheng:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.10/CC67

Topic: F.03. Motivation and Emotion

Title: Conditional knockout of ASIC1a in ASIC4-positive neurons reverses innate fear and anxiety phenotypes in ASIC4 KO

Authors: *Y.-C. CHIEN[1,2], S.-H. LIN[1], C.-C. CHEN[1,3];
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Abstract: ASIC4 is expressed in many nuclei in the CNS, however, its physiological function is still unclear. To probe the role of ASIC4, we generated an ASIC4-knockout/Cre-ERT2-knockin mouse line. Compared with wild-type littermates, ASIC4 knockouts showed higher levels of fear response (freezing) to the presence of 2,4,5-trimethylthiazoline (TMT), a synthetic analog of red fox feces; ASIC4 knockouts also demonstrated higher levels of anxiety-like behaviors in the OF and EPM task. These phenotypes were opposite to the ASIC1a knockout mice, which showed lower levels of TMT-induced fear and less anxiety-like behaviors in these two mouse anxiety tasks. Based on genetic mapping results, we hypothesized that ASIC4 in the CR/VIP-positive cortical interneurons (or the NG2-positive glia) might modulate innate fear and anxiety state by counteracting the membrane expression and thus the activity of ASIC1a. To test this working hypothesis, we first generated ASIC1a-/-::ASIC4-/- double knockouts and screened the phenotypes in the TMT, OF and EPM task. Results indicated that ASIC1a-/-::ASIC4-/- double knockouts showed ASIC1a-like phenotypes in the innate fear and anxiety tests. Further, we tested the hypothesis by breeding an ASIC4Cre-ERT2/+::ASIC1afloxed/floxed mouse line. After 14 days tamoxifen treatment, we screened the innate fear and anxiety phenotypes between ASIC4Cre-ERT2/+::ASIC1afloxed/floxed and ASIC4Cre-ERT2/+::ASIC1a+/+ mice. ASIC4Cre-ERT2/+::ASIC1afloxed/floxed mice demonstrated the same phenotypes as ASIC1a

conventional knockouts. Our conditional knockout results supported that ASIC1a in ASIC4-positive neurons is responsible for the fear/anxiety phenotypes.

Disclosures: **Y. Chien:** None. **S. Lin:** None. **C. Chen:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

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Program#/Poster#: 635.11/CC68

Topic: F.03. Motivation and Emotion

Title: Corticotropin-releasing factor modulates ultrasonic calling behavior and anxiety in rats

Authors: *J. O. TAYLOR, V. GJINI, A. LEMKE, B. G. COOPER;
TCU, Fort Worth, TX

Abstract: In a given year, 18% of the adult population in the United States will suffer from an anxiety disorder, and the rate increases to 29% over a person's lifetime. This prevalence rate illustrates the need to develop and improve therapeutic treatments for anxiety disorders. Toward that end, we seek to refine behavioral measures of anxiety in laboratory animals by determining whether specific vocalizations occur when animals are in an elevated state of anxiety. Rat ultrasonic vocalizations (USVs) broadly signal affective state. They can be categorized into one of two frequency ranges, 22 kHz or 50 kHz. The 22 kHz calls are more closely associated with negative affect states, whereas the 50 kHz range is associated with positive affective states. The 50 kHz range consists of calls that can be categorized into multiple subtypes; one USV subtype, flat calls, which are constant frequency 50 kHz (CF 50 kHz) calls, are not viewed as signaling a particular emotional state. We have been testing the novel hypothesis that these calls are promoted by anxiogenic situations. We tested this hypothesis using a behavioral paradigm where animals are introduced to a novel environment and then exposed to a series of six, temporally predictable, unsignalled footshocks (UFS). Exposure to the novel environment and initial footshocks is the anxiogenic component of the test, and the repeated footshocks should generate fear-related behaviors. In the UFS paradigm, rats initially produce CF 50 kHz calls (baseline and shocks 1-3) and then increase the production of 22 kHz calls following shocks 3-6. In the current experiment, rats were given intraventricular administration of corticotropin-releasing factor (CRF) or vehicle control 30 min prior to UFS testing. We hypothesized that CRF would increase CF 50 kHz USV production during the baseline and initial footshocks. Consistent with our hypothesis, during the UFS behavioral test, pretreatment with CRF increased CF 50 kHz USV production during the baseline and initial footshocks. During the testing, CRF administration

reduced rearing behaviors but not change freezing. Animals were subsequently tested on the elevated plus maze. CRF pretreatment decreased time spent in open arms compared to vehicle control infusion. These preliminary results provide further support for the hypothesis that CF 50 kHz USVs are produced when animals are in an elevated state of anxiety, and suggest that this USV classification provides a valuable behavioral measure for animal models of anxiety disorders.

Disclosures: J.O. Taylor: None. **V. Gjini:** None. **A. Lemke:** None. **B.G. Cooper:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.12/CC69

Topic: F.03. Motivation and Emotion

Support: TIFR, DAE

Title: Effects of acute pharmacogenetic activation of excitatory cortical neurons on anxiety and depressive-like behavior

Authors: *S. PATI, V. SINGH, V. VAIDYA;
Tata Inst. of Fundamental Res., Mumbai, India

Abstract: A balance between excitatory and inhibitory neurotransmission in local cortical microcircuits has been hypothesized to play a key role in adaptive stress responses. Such a balance of inhibition-excitation may also be important in the maintenance of a normal affective state. Recent results suggest that altering this balance within cortical microcircuits by acute pharmacogenetic inhibition of cortical inhibitory interneurons results in increased anxiety-like behavior (Soumier and Sibille, 2014). However, effects of direct activation of cortical excitatory neurons on anxiety and depressive-like behavior remain currently unknown. In the present study, we examined the effects of acute activation of neurotransmission within CamKIIα-positive excitatory neurons on anxiety and depressive-like behavior. We used a genetic strategy in mice to express the Gq coupled designer receptor exclusively activated by designer drugs (DREADD-hM3Dq) in cortical excitatory neurons of the forebrain using a Ca2+/ Calmodulin-dependent protein kinase II (CamKIIα) driver. Our results suggest that acute administration of the DREADD agonist clozapine-N-oxide (0.5 mg/ Kg) leads to decreased anxiety like behavior in the open field test, elevated plus maze and light-dark avoidance test. However, no apparent change in depressive-like behavior was observed in the tail-suspension test and forced swim test.

Future studies are aimed at investigating the role of increased excitatory neurotransmission through CamKIIα-positive neurons in mediating adaptive stress response.

Disclosures: S. Pati: None. **V. Singh:** None. **V. Vaidya:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.13/CC70

Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Title: Tau pathology induced anxiety symptoms through impairing vGAT-GABA system in mice hippocampus CA3

Authors: *X. LI[1], J. WANG[2];
[1]Key Lab. of Ministry of Educ. of Neurolo, HUBEI, China; [2]Pathophysiology Dept., Key Lab. of Ministry of Educ. of Neurolog. Dis., HUBEI, China

Abstract: Whether human tau pathology played a role in anxiety disorder in AD was unknown. Mice which were overexpressed with tau40-GFP on hippocampus CA3 showed significantly anxiety disorder. Abnormal neuronal network and impaired inhibitory tones were observed on CA3 regions. Extracellular GABA in CA3 decreased significantly in tau40 group on free-moving microdialysis test. We applied vGAT-ChR2 tg mice, optogenetically excited vGAT positive neurons impaired by tau in CA3 appeared obvious anxiolytic effect. In our study impaired GABA is related to the decline protein level of vGAT on tau infected mice. We used overexpression vGAT-RFP AAV, artificially restored vGAT level in CA3 could rescue tau induced anxiety behaviors. Collectively, these data reveal that tau pathology induced anxiety symptoms through impairing vGAT-GABA system in mice hippocampus CA3.

Fig 1

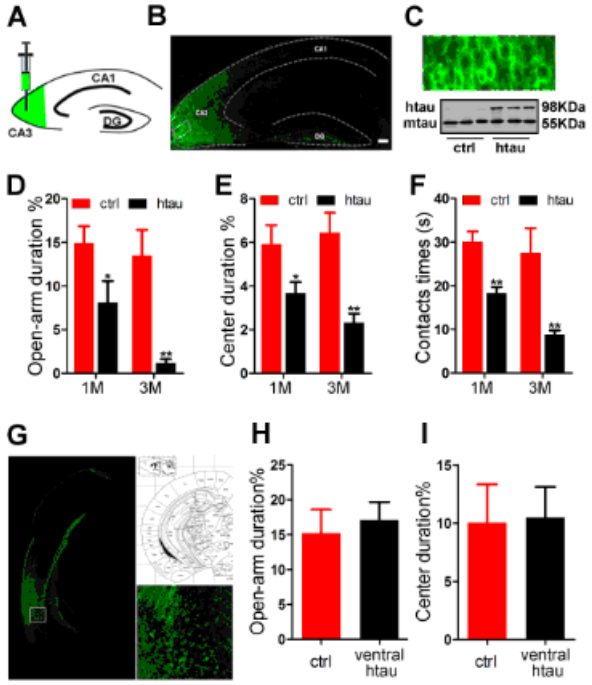


Fig 2

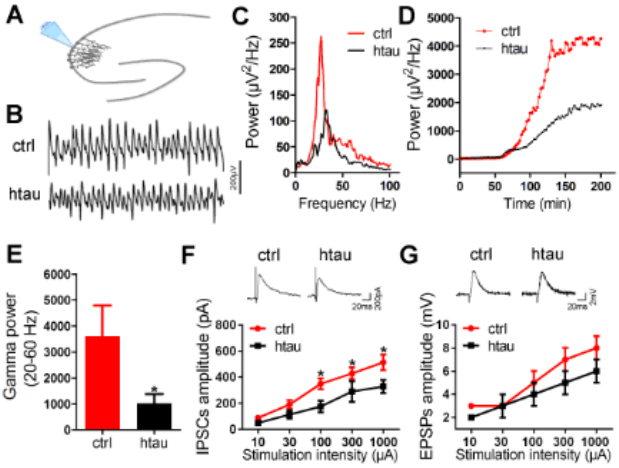


Fig 3

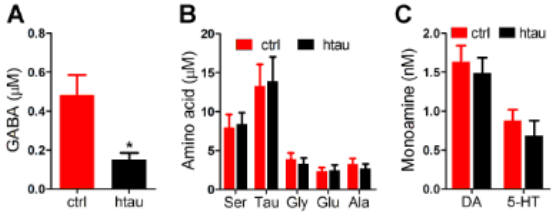
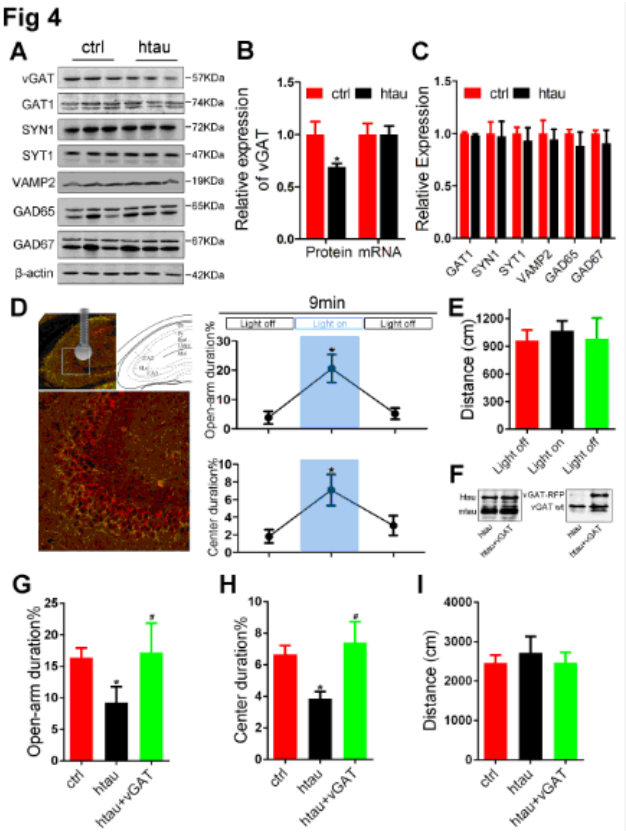


Fig 4



Disclosures: **X. Li:** None. **J. Wang:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.14/CC71

Topic: F.03. Motivation and Emotion

Support: ONR N000140910244

Title: Chronic administration of exogenous ketone supplementation reduces anxiety in Sprague-Dawley rats

Authors: ***C. ARI**, A. POFF, S. KESL, C. GOLDHAGEN, C. MURDUN, D. D`AGOSTINO; Mol. Pharmacol. and Physiol., Hyperbaric Biomed. Res. Laboratory, Univ. of South Florida, Tampa, FL

Abstract: Nutritional ketosis has proven effective for seizure disorders and other neurological disorders. Anecdotal reports suggest that nutritional ketosis can promote a reduction in anxiety. The focus of this study was to determine the effects of ketone supplementation on anxiety. We tested three exogenous ketone supplements fed chronically to Sprague-Dawley rats prior to assessment of anxiety measures. A total of 47 male Sprague-Dawley rats were fed for 83 days with either standard rodent chow (SD) or SD + ketone supplementation. Four treatment groups included low-dose ketone ester (1,3-butanediol-acetoacetate diester, 10g/kg/day, LKE), high dose ketone ester (25g/kg/day, HKE), beta-hydroxybutyrate-mineral salt (BHB-S), and BHB-S +medium chain triglyceride (BHB-S+MCT). Elevated plus maze (Coulbourn Instruments) was used to assess anxiety-related behavior of the rats. Behavioral data collection was conducted manually by a blinded observer and a video-tracking system (SMART V3.0 PLATFORM, Harvard Apparatus). Time spent (p=0.017;0.021, respectively) and distance traveled (p=0.03; 0.02, respectively) in open arms were significantly more in BHB-S and BHB-S+MCT groups, while time spent (p=0.011; 0.005, respectively) and distance traveled (p=0.002 in BHB-S group) in closed arms were significantly less in these groups, compared to control (SD). Latency to first entrance to closed arms was significantly higher in HKE, BHB-S and BHB-S+MCT groups (p=0.037; 0.035; 0.015, respectively). Blood ketone levels were elevated in all ketone supplement treatment groups similar to levels reported previously with a ketogenic diet. We conclude that chronic administration of exogenous ketone supplementation reduced anxiety in Sprague-Dawley rats.

Disclosures: **C. Ari:** None. **A. Poff:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of South Florida. **S. Kesl:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of South Florida. **C. Goldhagen:** None. **C. Murdun:** None. **D. D`Agostino:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); University of South Florida.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.15/CC72

Topic: F.03. Motivation and Emotion

Support: SIP 20140892

Title: Local administration of serotonin in the thalamic reticular nucleus induces anxiety in rat via 5HT1A receptor

Authors: *M. GARCIA-RAMIREZ, G. AVILA, B. DEL RIO;
ENCB-IPN, DF, Mexico, Mexico

Abstract: The Reticular Thalamic nucleus (RTn), a thin sheet of GABAergic neurons located between the external medullary lamina and the internal capsule of the thalamus, has been shown has a role to regulate flow of information between thalamus and cortex and serves a direct role in process of attention, arousal and sleep control (McCormick and Wang, 1991; Rodrigo-Angulo et al., 2008). RTn receive serotonergic projections from supralemniscal nucleus and express two major postsynaptic 5-HT receptors, 5-HT1A and 5-HT2A receptors, 5HT1A receptor being the most abundant (Rodriguez J et al., 2011). The local application of serotonin (5HT) at RTn suppress the burst firing of RTn neurons, resulting in single fire spike seen during arousal and attentive state. The first purpose of this study was to known the effect of 5HT application at RTn on anxiety behavior, the second purpose is explore if 5HT1A is related with these response. Rats were implanted unilaterally with a cannula in the RTn and infused with 5HT at different doses (1.17-117 nM). Anxiety was tested by the Shock Burying electrode Test (SBT), Elevated Plus Maze (EPM) and Social Interaction (SI). Motor activity was measured in automated activity counters after the end of SBT, EPM or SI. All doses of serotonin consistently produced anxiety, viewed as decreased in time in open arms and increased in time of frozen behavior in SBT and decreased time in SI. Motor activity was not affected with any dose. Anxiety induced by 5HT was reverted by previous administration of WAY 100635 (an antagonist 5HT1A). In conclusion these findings suggest a serotonergic involvement in anxiety via 5HT1A receptor. García-Ramirez M is fellow of COFAA

Disclosures: **M. Garcia-Ramirez:** None. **G. Avila:** None. **B. Del Rio:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.16/CC73

Topic: F.03. Motivation and Emotion

Support: CIHR MOP-130393

Title: Nucleus accumbens shell, but not core, regulates the expression of discriminative conditioned

Authors: *P. T. PIANTADOSI, D. C. M. YEATES, S. B. FLORESCO;
Psychology, Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Motivated behavior can be interrupted by the presentation of a previously conditioned, fear-inducing stimulus, a phenomenon known as conditioned suppression. The contribution of amygdala and prefrontal cortical circuitries to various aspects of conditioned fear and suppression has been well defined. The nucleus accumbens (NAc) is a major projection target of both of these regions, yet considerably less is known about the functional role of different accumbens subregions to aversive learning generally, and conditioned suppression specifically. Here we investigated whether two subregions of the NAc, the core (NAcC) and the shell (NAcS), are necessary for the appropriate discriminative expression of conditioned suppression. Male Long Evans rats were trained to lever press for sucrose reward on a VI-60 reinforcement schedule. They were then subjected to discriminative fear conditioning entailing eight, 30s presentations each of a CS+ (9kHz tone and flashing houselight terminating with 0.5mA/0.5s footshock) and a CS- (1kHz tone and continuous cue lights, no shock), without access to sucrose. Two days later, rats underwent an expression test session during which each CS was presented four times during VI-60 lever pressing for sucrose. The suppression of lever pressing during each CS served as the index of conditioned fear. Rats received inactivation (baclofen/muscimol; 75ng each/0.3µl saline per side) or saline infusion prior to the expression test phase of the task. Control rats in each condition (NAcC or NAcS) displayed appropriate discrimination, suppressing lever pressing during the CS+ exclusively. Inactivation of NAcS dramatically reduced conditioned suppression during CS+ presentation, but did not induce a non-specific disinhibition of lever pressing. In comparison, inactivation of NAcC had no impact on the ability to appropriately suppress appetitive responding in the face of an aversive stimulus, but did reduce food-seeking behavior as measured by a reduction in lever pressing. These results are in keeping with the particular role for NAcS, but not NAcC, in response inhibition and suggest that, in addition to facilitating certain aspects of reward-related behavior, the NAcS also plays a key role in reorganizing behavior in response to aversive stimuli. Given that we and others have reported a similar effect following prelimbic (PL) medial prefrontal cortex inactivation, future experiments will attempt to dissect this potential circuit level interaction.

Disclosures: P.T. Piantadosi: None. **D.C.M. Yeates:** None. **S.B. Floresco:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.17/CC74

Topic: F.03. Motivation and Emotion

Support: Canadian Institutes of Health Research Grant MOP89758 to GJK.

National Key Technology Research and Development Program of China Grant 2013BAI08B02 to YL

Title: Blocking of orexin receptors in the paraventricular thalamus has no effect on conditioned fear but has anxiolytic effects

Authors: X. DONG[1], S. LI[1], Y. LI[2], *G. J. KIROUAC[1];
[1]Oral Biol. and Psychiatry, Col. of Dent., Winnipeg, MB, Canada; [2]Key Lab. of Mental Hlth., Inst. of Psychology, Beijing, China

Abstract: Fear is an emotional response to an imminent danger whereas anxiety is a response to an unknown threat. The paraventricular nucleus of the thalamus (PVT) projects strongly to the central nucleus of the amygdala that contains the neurons that produce the coordinated fear response and recent experimental evidence indicates a role for the PVT in conditioned fear. Furthermore, the PVT receives a dense orexin input, a neuropeptide that regulates arousal, and injections of orexin antagonists in the PVT have anxiolytic effects. The present study was done to determine if administration of a dual orexin receptor antagonist (DORA) in the region of the PVT interferes with the expression of fear in rats conditioned using cued or contextual paradigms. In the cued conditioning experiment, rats were exposed to six 0.65 mA 0.5 s footshocks co-terminating with tones (70 dB at 5 kHz for 30 s). Twenty four hours later, fear expression (freezing) to the tone alone was measured after the infusion of different doses of the DORA in the PVT. In the contextual conditioning experiment, rats were exposed to five 1.5 mA 5 s footshocks over 10 min. Twenty four hours later, fear expression to the shock context was assessed in rats that received infusion of the DORA in the PVT. Two weeks later, the contextual conditioned rats were used to determine if the DORA has anxiolytic effects in the social interaction and open field tests. Infusion of 0.5 µl of a DORA named N-biphenyl-2-yl-1-{[(1-methyl-1H-benzimidazol-2yl)sulfanyl] acetyl}-L-prolinamide at a concentration of 0.1, 1.0, and 10 nmol had no effect on the freezing produced by the auditory cue or the context previously associated with footshocks. In contrast, the 1.0 and 10 nmol doses were anxiolytic in the social interaction test but not in the open field test. The results of the present study do not support a role for orexin receptors in the PVT in the expression of cued or contextual learned fear. The finding that blocking of orexin receptors in the PVT region reduces anxiety is consistent with other studies indicating a role for orexins in the PVT in anxiety-like behaviors.

Disclosures: X. Dong: None. **S. Li:** None. **Y. Li:** None. **G.J. Kirouac:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.18/CC75

Topic: F.03. Motivation and Emotion

Support: European Community's Seventh Framework Programme (FP7/2007-2013) / ERC grant agreement n° 311701

Title: A neuropeptidergic trace of acute stress in a central fear circuit switches active to passive coping strategies

Authors: *P. PLIOTA[1], F. GRÖSSL[1], V. BÖHM[1], J. GRIESSNER[1,2], W. HAUBENSAK[1]; [1]Res. Inst. of Mol. Pathology (IMP), Vienna, Austria; [2]Med. Univ. of Vienna, Vienna, Austria

Abstract: Survival critically depends on optimizing behavioral strategies for avoiding threats. Animals learn from aversive experiences that specific cues predict danger and best be avoided. In the absence of such discrete cues, however, the threat remains unpredictable. In these cases the animal adapts by switching from active to more passive behaviors. Here, we developed a behavioral paradigm to study these behavioral effects of acute stress on subsequent environmental challenges on mice. We used molecular, pharmaco-, optogenetic and electrophysiological methods to dissect the underlying mechanisms in central amygdala (CE) - a key structure for fear behaviors. Quantitative cholera toxin B retrograde tracing identified the paraventricular thalamus (PVT) - a structure being implicated in stress - as one of the major inputs to the CE. Site-specific lesions and projection-specific optogenetic manipulation indicated that the PVT-CE connection is involved in behavioral effects of acute stress. Combining electrophysiology with optogenetics, we observed that PVT asymmetrically innervates two antagonistic circuits in CE. Our data support the notion, that acute stress experience activates PVT-CE projections and releases a local neuropeptidergic signal, that modulates circuit dynamics in a synergistic manner, leading to a switch from active to passive coping behaviors.

Disclosures: P. Pliota: None. **F. Grössl:** None. **V. Böhm:** None. **J. Griessner:** None. **W. Haubensak:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.19/CC76

Topic: F.03. Motivation and Emotion

Support: NSERC Grant 288348

Title: Effects of CB1 receptor agonism and antagonism on fear and stress responses in adult intact, ovariectomized, and estradiol-treated female rats

Authors: *J. J. SIMONE[1], B. L. MALIVOIRE[2], C. M. MCCORMICK[3];
[1]Biol. Sci., Brock Univ., St Catharines, ON, Canada; [2]Psychology, Biol., [3]Psychology, Brock Univ., St. Catharines, ON, Canada

Abstract: We have previously reported differential effects of CB1 agonism on unconditioned (innate) and conditioned fear in adult male rats (Simone et al., 2015). How CB1 regulates fear in females, however, is largely unknown. **In experiment 1**, we investigated the effects of the highly selective CB1 agonist ACEA (0.1 mg/kg and 0.01 mg/kg) and antagonist AM251 (1 mg/kg) on fear and stress responses in adult intact female rats (N = 60). AM251 increased anxiety-like behaviour in the elevated plus maze (decreased time on the open arm relative to ACEA and vehicle, all $p < 0.05$). ACEA was without effect. In the open field test, 0.01 mg/kg ACEA decreased anxiety-like behaviour (increased time in the centre) compared to all other groups (all $p < 0.04$). AM251 impaired locomotor activity (decreased distance travelled) compared to 0.01 mg/kg ACEA ($p = 0.013$) and vehicle ($p = 0.036$). When tested 24 hours after fear conditioning (3 tone-shock pairings, 1 minute ITI), neither ACEA nor AM251 affected generalized fear to a novel context or recall of the conditioned fear. AM251 and 0.1 mg/kg ACEA impaired, and 0.01 mg/kg ACEA enhanced, fear extinction. AM251 increased plasma corticosterone after fear extinction compared to 0.1 ($p = 0.02$) and 0.01 ($p = 0.005$) mg/kg ACEA and vehicle ($p = 0.06$). **In experiment 2**, adult ovariectomized rats (N = 108) were treated with sesame oil or 17β-Estradiol either 6 or 48 hours before behavioural testing. Irrespective of hormone treatment, AM251 decreased time spent on the open arms of the EPM relative to 0.01 mg/kg ACEA ($p = 0.03$) and vehicle ($p = 0.001$). Neither hormone nor drug had an effect on anxiety-like behaviours in the open field. There was an effect of hormone and drug on locomotor activity; estradiol increased distance travelled compared to oil ($p = 0.005$), and AM251 decreased distance travelled compared to vehicle ($p = 0.03$) and ACEA ($p = 0.002$). When tested 24 hours after fear conditioning, AM251 decreased generalized fear to a novel context compared with vehicle ($p = 0.01$) and ACEA ($p = 0.06$). Neither hormone nor drug had any effect on recall or extinction of the previously conditioned fear, however, both ACEA and AM251 increased fear-induced corticosterone concentrations compared to vehicle (all $p < 0.02$). These results provide evidence for sex-differences in CB1 regulation of fear and stress. ACEA had no effect in females at a dose effective in male rats, and only modest effects at a lower dose. Despite no evidence of estradiol modulating the effects of ACEA or AM251, gonadal status appears to be a contributing factor given the differences between intact and ovariectomized females.

Disclosures: **J.J. Simone:** None. **B.L. Malivoire:** None. **C.M. McCormick:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.20/CC77

Topic: F.03. Motivation and Emotion

Support: R15MH104485

P20 RR15567

CBBRE Pilot Grant

Anonymous Donor

Title: Endocannabinoid receptor CB_2 gene expression in hippocampus reflects modulation of anxious behavior

Authors: *J. ROBERTSON[1,2], J. K. ACHUA[1,2], J. P. SMITH[1,2,4,6,7], M. A. PRINCE[1], T. R. SUMMERS[1], P. J. RONAN[5,8,2,3], C. H. SUMMERS[1,2];
[1]Biol., Univ. of South Dakota, Vermillion, SD; [2]Neurosci. Group, [3]Dept. of Psychiatry, Sanford Sch. of Med., Vermillion, SD; [4]Sioux Valls VA Hlth. Care Syst., [5]Sioux Falls VA Hlth. Care Syst., Veterans Affairs Res. Service, Sioux Falls, SD; [6]Inst. of Possibility, Sioux Falls, SD; [7]Sanford Hlth., Sioux Falls, SD; [8]Avera Res. Ctr., Sioux Falls, SD

Abstract: Anxiety is expressed across a continuum of stressful and/or fearful intensity, with varying impacts on decision-making successfully measured in the Stress Alternatives Model (SAM). Recent legislation in many states and countries has led to the widespread availability of cannabinoids for use by people suffering from anxiety-spectrum disorders, but research on their actions and efficacy in such therapies is lacking. It has become apparent that the hippocampus plays a role in more than just certain forms of memory, but also in affective behavior, emotion, and anxiety regulation. Research suggests this may occur through endocannabinoid mediation of long-term depression (LTD) in hippocampal pyramidal cells. Hippocampal lesions cause behavioral disinhibition and anxiolysis. The specific location of CB_1/CB_2 receptor action could be important in determining emotional valence, as the ventral and dorsal hippocampal subregions project to different brain areas and have different functions. Whereas the dorsal hippocampus is involved in spatial memory and cognition, the ventral hippocampus, with projections to the PFC, BNST, amygdala, and HPA axis, is important for the emotional response to stress. However, the expression of CB_1 and CB_2 receptors in the hippocampus following anxiogenic and anxiolytic activities remain unknown. During repeated social defeat in a Stress-Alternatives Model arena

(SAM; an oval open field with escape portals only large enough for smaller animals), smaller C57BL6/N mice are subject to fear conditioning (tone = CS), and attacked by novel larger aggressive CD1 mice (US) over four daily (5 min) trials. Each SAM trial presents an opportunity for escape or submission, with stable behavioral responses established by the second day of interaction. Additional groups had ad-libitum access to a running wheel for the duration of the experiment. Gene expression of CB_1 and CB_2 were measured in conditioned animals which escaped social aggression, submitted to social aggression, and no-aggression controls. Anxiogenic activity, such as social aggression, stimulates CB_2 gene expression in the dorsal CA_1, dorsal and ventral dentate gyrus subregions in animals displaying a submissive behavioral phenotype. Escape behavior is anxiolytic, and reduces CB_2 expression in the dorsal CA_1 region. Exercising mice subjected to social aggression demonstrate an increase in CB_2 mRNA in dorsal DG/CA_1 in both escaping and submitting animals. These results suggest that the CB_2 receptor system is upregulated during anxiogenic social interactions, but also by exercise; both responses may prove to be prophylactically adaptive.

Disclosures: **J. Robertson:** None. **J.K. Achua:** None. **J.P. Smith:** None. **M.A. Prince:** None. **T.R. Summers:** None. **P.J. Ronan:** None. **C.H. Summers:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

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Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.21/CC78

Topic: F.03. Motivation and Emotion

Support: NCCIH R15AT008060

Title: Understanding the role of serotonin receptor subtypes 7 and 2C (5-HT7/2C) in comorbid pain and depression using novel compounds derived from marine cyanobacteria

Authors: ***N. C. LAX**, C. M. IGNATZ, E. J. HILTON, T. AHMED, K. J. TIDGEWELL, B. J. KOLBER;
Duquesne Univ., Pittsburgh, PA

Abstract: Chronic pain and major depressive disorder are widespread conditions in the United States. Interestingly, these conditions often occur comorbidly, with each individual disease amplifying the symptoms of the other. Many medications available on the market today for treating pain or depression target G-protein coupled receptors (GPCRs), implying that this class of receptors may be involved in the treatment of the comorbidity of these conditions. Our efforts

have sought to characterize two poorly understood GPCRs, the serotonin receptor subtypes 7 and 2C (5-HT7/2C), and the role that they play in comorbid pain and depression. Our approach for targeting these receptors uses compounds isolated from filamentous marine cyanobacteria collected from the Las Perlas Archipelago off of the coast of Panama in the Pacific Ocean. Compounds from this cyanobacterial collection show strong affinity for the 5-HT7 and 2C receptors. These compounds were screened for *in vivo* activity using a series of pain and depression behavioral assays. Compounds were delivered into male C57Bl/6J mice via intra-cerebroventricular (ICV) cannulas or injections into regions of the brain with high expression of these receptors. Compounds were tested in naïve mice or in mice subjected to a model of comorbid pain and depression, the Spared Nerve Injury (SNI) surgery. SNI surgery involves ligating two of the three branches of the sciatic nerve, the tibial and common peroneal branches, while leaving the third branch, the sural branch, intact. SNI surgery induces mechanical hypersensitivity in the ipsilateral paw (modeling pain) and also induces depression-like behavior. We have found that administration of compounds isolated from marine cyanobacteria induce effects in several standard behavioral assays. Our results suggest that cyanobacteria produce compounds with neural effects that may be useful in understanding pain and depression.

Disclosures: **N.C. Lax:** None. **C.M. Ignatz:** None. **E.J. Hilton:** None. **T. Ahmed:** None. **K.J. Tidgewell:** None. **B.J. Kolber:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 635.22/DD1

Topic: F.03. Motivation and Emotion

Support: NIH Grant MH-086727

Title: Differential contribution of amygdala GABAA receptors in benzodiazepine-induced anxiolysis

Authors: *Y. GAO, S. HELDT;
Anat. and Neurobio., Univ. of Tennessee Hlth. Sci. Ctr., Memphis, TN

Abstract: Over the past decade significant advances were made in understanding the differential roles GABAA receptor (GABAAR) subtypes play in various behaviors, including anxiety. At present, it is generally believed that α2-subunit containing GABAARs (α2-subtypes) are responsible for benzodiazepine (BZ) -induced anxiolysis. However, there is some evidence

suggesting that α1- and α3-subtypes might also mediate anxiolysis. To help clarify this issue, we have examined the anxiolytic-like effects of various subtype-selective and non-selective GABAAR agonists/antagonists given to wildtype C57BL/6J (WT) mice and point-mutation mice expressing BZ-insensitive GABAARs. In these experiments, drugs were administered either systemically or via microinfusion in the basal lateral amygdala (BLA), a brain region which putatively mediates BZ-induced anxiolysis. After administration, mice are tested on the elevated-plus maze (EPM) where various behavioral markers of anxiety are obtained. Here we report some of our initial findings. In line with previous findings, systemic injections of the non-selective BZ chlordiazepoxide (CDP) induced robust anxiolytic-like effects in WT mice. These effects were potentiated in α1(H101R) mice, reduced in α3(H126R) mice, and ablated in α2(H101R) mice. Similarly, preliminary results showed intra-BLA microinfusion of CDP produced anxiolytic-like effects in α1(H101R) and α3(H126R) mice, but not α2(H101R) mice. Systemic injections and intra-BLA microinfusion of a α1-selective agonist (zolpidem) in WT mice produced slight anxiolytic-like effects at lower doses. Systemic injection and intra-BLA microinfusion of a reportedly putative α3-selective agonist TP003 produced marked anxiolytic-like effects in WT mice. Taken all together, these initial results suggest that both α2- and, to a certain degree, α3-GABAAR subtypes contribute to the BZ-induced anxiolysis and that the BLA is a major brain region mediating these effects. On the other hand, α1-subtypes are less involved in anxiolysis. The potentiated effects of CDP in α1(H101R) mice may be due to the increase availability of CDP to α2- and α3- subtypes in the absence of BZ binding to α1-GABAAR subtypes. We are currently in the process of 1) investigating whether selective antagonism of α1-subtypes can rescue the blunted anxiolytic-like effects of BZ in α2(H101R) mice; 2) investigating the effects of TP003 in α2(H101R) and α3(H126R) mice; and 3) utilizing multivariate analysis and computational methods to generate a quantitative model of each subtype's contribution to BZ-induced anxiolytic-like effects.

Disclosures: **Y. Gao:** None. **S. Heldt:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

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Ontario Mental Health Foundation

Title: Induction of compulsive checking with quinpirole and 8-OH-DPAT as a perturbation of security motivation: dose-response profiles

Authors: *H. SZECHTMAN, A. DVORKIN-GHEVA, A. H. ALKHATIB, M. C. TUCCI; McMaster Univ., Hamilton, ON, Canada

Abstract: A prior report showed that both the dopamine D2/D3 receptor agonist quinpirole and the serotonin 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) can induce compulsive checking in rats, with 8-OH-DPAT producing a seemingly stronger effect than quinpirole. However, the report was a single dose study, and hence the obtained findings may reflect a dose-effect rather than indicating that "8-OH-DPAT and quinpirole produce compulsive behavior by acting on different parts of a security motivation circuit underlying OCD" [1]. Here, we used a range of doses for quinpirole and 8-OH-DPAT to induce compulsive checking and generate full dose-response profiles. Male Long-Evans rats (n=167) received twice per week for 5 weeks either 8-OH-DPAT (0, 0.03, 0.125, 0.25, 1 mg/kg) or quinpirole (0, 0.03125, 0.0625, 0.125, 0.25, 0.5 mg/kg) and after each injection introduced into a large open field (160 x 160 cm) for 55 min where their behavior was video recorded. Spatial coordinates of the rat's location in the open field were extracted at a rate of 30 fps by EthoVision software and used to derive measures of compulsive checking with custom software. Results indicated that induction of compulsive checking was faster with 8-OH-DPAT than quinpirole and that for some measures of performance the function describing the relationship between drug dose and response had different parameters for quinpirole and 8-OH-DPAT. Findings are consistent with the suggestion that quinpirole may induce compulsive checking behavior by directly driving dopaminergic activity mediating the motivational drive to check. Conversely, 8-OH-DPAT may perpetuate the activated motivational state by inhibiting the serotonergic negative feedback signals that normally deactivates security motivation and the OCD circuit. [1]. Alkhatib, A. H., Dvorkin-Gheva, A., & Szechtman, H. (2013). Quinpirole and 8-OH-DPAT induce compulsive checking behavior in male rats by acting on different functional parts of an OCD neurocircuit. *Behavioural Pharmacology, 24*(1), 65-73. doi:10.1097/FBP.0b013e32835d5b7a

Disclosures: H. Szechtman: None. **A. Dvorkin-Gheva:** None. **A.H. Alkhatib:** None. **M.C. Tucci:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: VA Merit Award IO1BX001978

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Title: Blunted HPA-axis response is not sufficient to predict a complex PTSD-like behavioral phenotype

Authors: *A. I. VAZDARJANOVA[1,2], D. CRETHERS[4], K. BUNTING[2], R. NALLOOR[4], A. OHRI[4], T. PATTON[3];
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Abstract: Post-Traumatic Stress Disorder (PTSD) may occur after a person is exposed to one or more highly traumatic events. Some of its hallmark characteristics are hyperarousal and anxiety, and many sufferers have impaired learning of safety (fear extinction). These maladaptive responses can lead to impaired social and cognitive functioning. Not all individuals who have experienced a traumatic event will develop PTSD; this is evidence that individual susceptibility to PTSD exists. The predictive factors, however, are poorly understood. To address this gap in knowledge, we previously reported a unique behavioral model to identify rats susceptible to PTSD-like behaviors prior to emotional trauma. In our model Susceptibility is assessed as elevated acoustic startle response (ASR) AND anxiety-like behavior in the elevated plus maze (EPM) 4 days following brief exposure to a mild stressor (cat hair). Measured PTSD-like behaviors are fear extinction after contextual fear conditioning and a second ASR three weeks after the initial ASR. Comparing Lewis and Sprague-Dawley (SD) rats in our model we tested the hypothesis that a disregulated HPA axis is sufficient to predict a PTSD-like behavioral phenotype. Lewis rats are known to have blunted corticosterone release in response to predator stress, compared to SD rats. Therefore, we hypothesized that a higher percentage of Lewis rats will be preclassified as susceptible to impaired fear extinction and in long-lasting elevated ASR. Contrary to our hypothesis, a similar percentage of Lewis and SD rats were classified as susceptible, although all Lewis rats had fewer contacts with the mild stressor. Although the ASR was comparable between the two strains, Lewis rats were more likely to enter the open arms of the EPM. Importantly, Lewis rats were twice as likely to show impaired extinction compared to SD rats (66% vs. 33%). Also, Lewis rats showed no evidence for lasting elevated ASR. There were no significant strain differences in performance on the spatial probe test and reversal probe test in the Morris water maze. These data suggest that a disregulated HPA axis is not sufficient to predict a complex PTSD phenotype and is not likely to be a useful predictive factor for susceptibility. Together with previous work with humans and with animal models of PTSD showing that high levels of corticosteroids immediately before or shortly after trauma decrease the probability of developing PTSD, the current findings make an important contribution in dissociating predictive vs contributing factors for developing PTSD.

Disclosures: **A.I. Vazdarjanova:** None. **D. Crethers:** None. **K. Bunting:** None. **R. Nalloor:** None. **A. Ohri:** None. **T. Patton:** None.

Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

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Topic: C.16. Cognitive, Emotional, and Behavioral State Disorders

Support: 5 T32 GM007337

Title: Proteomic profile changes in SAPAP3-deficient mice

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Abstract: SAP90/PSD95-associated protein 3 (SAPAP3), a postsynaptic density scaffolding protein enriched in glutamatergic synapses in the striatum, is thought to play a role in regulating synaptic function and plasticity. Rare variants in the gene encoding SAPAP3 have been implicated in obsessive-compulsive disorder (OCD), Tourette syndrome, and trichotillomania. These disorders are thought to involve dysregulated cortico-striatal circuits, and dysfunction of these circuits is evident in SAPAP3-deficient mice. SAPAP3-deficient mice display compulsive grooming behavior, as well as increased anxiety-like behavior. These mice have altered composition of striatal postsynaptic glutamatergic receptors, but the mechanism by which this occurs is not well understood. To further characterize how SAPAP3 deficiency affects behavior, we compared the striatal proteome of a SAPAP3 deficient mouse to its wild type littermate. Using two-dimensional gel electrophoresis and mass spectrometry we identified candidate proteins, including cytoskeletal-associated proteins and proteins involved in cell guidance, myelination, and vesicle endocytosis. From this list we hope to identify targets and pathways involved in the pathological grooming and anxiety-like behavior of SAPAP3-deficient mice.

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Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

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ON.2—O NOVO NORTE—North Portugal Regional Operational Programme 2007/2013, of the National Strategic Reference Framework (NSRF) 2007/2013, through the European Regional Development Fund (ERDF)

Title: Epigenetic control of post-natal neuroplasticity in the healthy and stressed brain: exploring methylation and hydroxymethylation marks

Authors: *A. MATEUS PINHEIRO[1,2], M. SANTIAGO[1,2], P. PATRICIO[1,2], J. MARINHO[1,2], M. BRANCO[3], N. ALVES[1,2], A. MACHADO SANTOS[1,2], M. MORAIS[1,2], J. CORREIA[1,2], C. ANTUNES[1,2], J. BESSA[1,2], W. REIK[4], N. SOUSA[1,2], J. MARQUES[1,2], L. PINTO[1,2];
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Abstract: The adult central nervous system (CNS) is endowed with considerable regenerative and neuroplastic potential. Neuroplasticity, in its different forms, is dynamically modulated by intrinsic genetic factors in conjugation with environmentally imposed factors of our everyday life. Nowadays, stress-exposure is a common environmental etiological factor leading to various pathological marks in neurochemical and neuroplastic phenomena, many of them underlying the so-called stress-related disorders. Moreover, several studies have shed light on how epigenetic mechanisms serve as mediators of the pathological effects of stress on brain homeostasis. Here, we aimed to study the effects of stress on the epigenetic landscapes of the dorsal and ventral hippocampal dentate gyrus (DG). Furthermore, we aimed to explore how chronic exposure to stress impacts on the DG epigenome and its repercussions to fundamental emotional and cognitive modalities. We have exposed young-adult Wistar-Han rats to a pre-validated unpredictable chronic mild stress (uCMS) protocol during 6 weeks and performed a battery of behavioral tests to analyze emotional and cognitive dimensions. After sacrifice, we have analyzed citogenesis and dendritic morphological rearrengements. In addition, we have conducted genome-wide analysis of methylation and hydroxymethylation in these areas. So far, results demonstrate that stress exposure compromises different neuroplastic processes, affecting different behavioral dimensions. Moreover, hydroxymethylation pathways are likely to be

involved in the pathological effects of stress exposure, as they are differentially regulated in control and stress-exposed animals.

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Poster

635. Fear and Anxiety: Molecular and Cellular Mechanisms

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VA Merit IO1 BX001374

Title: Increased amygdalar glutamate efflux in response to predator stress is modulated by mu opioid receptors

Authors: *A. C. SHARKO, J. PARILLA-CARRERO, K. F. KAIGLER, D. LEE, G. HARTSHORN, J. R. FADEL, M. A. WILSON;
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Abstract: Exposure to predator cues is a form of traumatic stress used as a rodent model of PTSD-like changes in behavior. The central nucleus of the amygdala (CeA) plays an important role in aversive and fear behavioral responses, including responses induced by predator exposure in rats. Previous studies in our lab demonstrated that predator stress activates distinct neuronal populations in the amygdala (Butler et al., 2011) and pharmacological alteration of mu opioid receptor (MOR) activity in the CeA shaped the behavioral responses induced by ferret odor (Wilson & Junor 2008). The present study investigated endocrine and amygdalar responses to predator stress, and if pharmacological manipulation of MOR in the CeA changed glutamate and GABA released *in vivo* in response to ferret odor using *in vivo* microdialysis. Ferret odor exposure increased glutamate, but not GABA, efflux in the CeA in a manner that was dependent upon presynaptic release, since it was blocked by tetrodotoxin. Further, the increases in CeA glutamate release were positively correlated with freezing behavior, and negatively correlated with grooming behavior during the initial period (15 min) of ferret odor exposure. Interestingly,

we found that glutamate efflux elicited by ferret odor exposure was blocked by infusion of the MOR antagonist CTAP into the CeA. Infusion of the MOR agonist DAMGO into the CeA did not alter glutamate efflux in response to ferret odor, but DAMGO-treated rats showed exaggerated fear responses to ferret odor. Ferret odor exposure combined with DAMGO infusion also induced significant neuronal activation in the bed nucleus of the stria terminalis (BNST) as assessed by cFos immunoreactivity. In the vehicle treated groups, there were correlations between neuronal activation in the BNST and ventrolateral septum with fear defensive responses. These results suggest that glutamate efflux in the CeA and activation of the CeA-BNST circuit plays a modulatory role in determining the magnitude of behavioral responses predator threat, and that activation of MOR in the central amygdala may help shape behavioral responses to predator stress. Additional studies using indwelling jugular catheters also showed ferret odor exposure increased circulating levels of corticosterone, but not NPY. Completion of these studies will allow correlations between the observed endocrine changes and behavioral responses to ferret odor (freezing).

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Poster

636. Motivation and Emotion: Reward II

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Support: NIMH Grant K01MH096175-01

NARSAD Young Investigator Award to WKS

NIMH IRP

NIDDK IRP

Title: Mid-insula activity to food vs non-food images is positively correlated with hunger susceptibility

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Abstract: Individuals differ in their interoceptive sensitivity to hunger sensations. To date, however, relatively little is known about which brain regions underlie the relationship between hunger susceptibility and appetitive responses to food cues. We thus assessed subjects' self-reported hunger susceptibility, and then subsequently asked the subjects to undergo an fMRI scan during which they viewed food and non-food photographs. We then examined the relationship between activity during the food/non-food picture task and hunger susceptibility. Thirty-two right-handed healthy adults completed the Three Factor Eating Questionnaire (TFEQ), a self-report measure that includes a so-called 'Hunger' subscale measuring susceptibility to sensations of hunger. Later, subjects underwent fMRI while performing a task in which they viewed food and non-food objects while making repetition detection judgments. There was a wide distribution of body mass indices across subjects, and all were screened to exclude the presence of metabolic diseases. Additionally, at the time of scanning subjects were in a eucaloric state, and had eaten two hours prior to scan session. Echoplanar imaging was collected with a 3T MRI scanner and a 16-channel head coil. A random effects paired sample t-test revealed that viewing foods relative to non-foods was associated with bilateral activity throughout regions implicated in appetitive responses to food, including the anterior and mid-insula, orbitofrontal cortex, amygdala, as well as the ventral striatum. Of critical importance to the present study, random effects group analyses of the imaging data also indicated that subjects' ratings on the TFEQ hunger subscale were positively correlated with activity bilaterally in the dorsal mid-insula cortex ($p < .05$ corrected for multiple comparisons). Individuals who report high hunger susceptibility also exhibit greater activity in the dorsal mid-insula to food images, relative to non-food images. This is significant as this region is thought to serve as a conduit for integrating appetitive and affective information with interoceptive signals about the state of the body. For example, responses in this region of the insula to food pictures are sensitive to interoceptive cues of peripheral energy availability (e.g., circulating glucose) and activity within this region has been shown to underlie interoceptive attention to visceral sensations.

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Poster

636. Motivation and Emotion: Reward II

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Topic: F.03. Motivation and Emotion

Title: Effects of increasing adult hippocampal neurogenesis in mice during exposure to chronic stress

Authors: L. CULIG[1,2], S. LEGENDRE[1,2], F. MINIER[1,2], *G. GRIEBEL[3], A. SAHAY[4,5], R. HEN[6], C. BELZUNG[1,2];
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Abstract: Local changes in the hippocampal network (addition of new neurons in the dentate gyrus) might change the activity of neural circuitry in the areas to which the hippocampus projects. Among those structures are the mPFC (medial prefrontal cortex), amygdala and nucleus accumbens (NAc). For example the NAc, which has a crucial role in reward and motivation, receives an input from the CA1 and ventral subiculum of the hippocampus that depolarizes the cells in the NAc, making them more excitable. Interestingly, the size of the hippocampus and more specifically the number of adult newborn granule cells, are decreased by unpredictable chronic mild stress (UCMS). Further, one of the notable effects of chronic stress is the induction of ΔFosB in the NAc, an unusually stable transcription factor which belongs to the Fos family of proteins, but unlike other members of the family, accumulates over time after repeated stress exposure. This accumulation has been observed in many animal models of depression, including UCMS, and it could be the basis of certain behavioral consequences of exposure to chronic stress. This ΔFosB induction could have a protective role against stress, but no studies so far have explored how a specific increase in neurogenesis regulates the induction. We investigated the role of increasing adult hippocampal neurogenesis on stress-related behavior (with a focus on behaviors where NAc is implicated) and the functional brain circuitry involved, in mice exposed to UCMS. We used iBax mice, in which the pro-apoptotic gene Bax was selectively ablated in neural stem cells, therefore inducibly enhancing survival and functional integration of newborn neurons in the adult brain after tamoxifen administration. In order to investigate the role of adult neurogenesis in remission after UCMS, the animals were exposed to UCMS for 8 weeks, and treated with tamoxifen 3 weeks after the beginning of the UCMS to induce increased neurogenesis. In week 8, they were submitted to a battery of behavioral tests to assess depressive-like and anxiety-like behavior, with a specific focus on tests assessing anhedonia, which is related to the NAc. In week 9, blood was collected to assess basal corticosterone levels, and the animals were sacrificed and their brain either collected for ΔFosB and c-Fos immunohistochemistry or used for dissection of brain areas of interest (NAc, mPFC and Amy).

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Poster

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Title: Role of inhibitory signaling in the nucleus accumbens during reward-seeking behavior

Authors: *S. E. MORRISON[1], V. B. MCGINTY[1,2], J. DU HOFFMANN[1,3], S. M. NICOLA[1]; [1]Psychiatry, Albert Einstein Col. of Med., Bronx, NY; [2]Neurobio., Stanford Univ., Palo Alto, CA; [3]Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: The nucleus accumbens (NAc) contains many neurons that respond with phasic increases or decreases in activity to a reward-predictive cue. Cue-evoked excitations have been shown to encode motivational significance, locomotor properties such as latency to approach a reward-associated target, and, more recently, spatial location with respect to the target. However, little is known regarding the functional significance of cue-evoked inhibitions in reward-seeking behavior. We have recently shown that these inhibitions - unlike cue-evoked excitations - are not modulated by dopamine, suggesting that they may play a distinct role in subjects' decision to approach a reward-related object. In order to determine what information is encoded by cue-evoked inhibitions during reward-seeking behavior, we analyzed the activity of individual NAc neurons recorded during two tasks: 1) a discriminative stimulus (DS) task in which rats responded to an auditory cue with a lever press in order to obtain sucrose reward and 2) a decision-making task in which the auditory cue signaled the availability of a choice between levers, while the reward size, effort requirement, and target locations associated with the levers were systematically varied. Importantly, both tasks involve flexible approach to the reward-

associated target, ensuring that NAc activity is required for task performance. Consistent with prior studies, many neurons had activity that was modulated by cue presentation, including 127 neurons (21%) with significant cue-evoked inhibitory responses (out of 607 cells recorded in 30 rats). We found that these inhibitions, similar to cue-evoked excitations, encode expectation of reward: they respond more strongly (i.e., are more inhibited) to a cue that predicts reward than an unrewarded cue. Unlike excitations, however, cue-evoked inhibitions consistently encode reward size: they respond more strongly to a cue that predicts large reward than one that predicts small reward. In contrast, cue-evoked inhibitions rarely encode expected effort, despite the frequently hypothesized role of the NAc in promoting effort exertion to obtain reward. Finally, we found that inhibitions, like excitations, are strongly modulated by spatial proximity to a rewarded target, indicating that they could play a role in gating or promoting approach to nearby reward-associated objects.

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Poster

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Topic: F.03. Motivation and Emotion

Support: CIHR

Concordia University

Title: Dopamine and Pavlovian conditioning: studies using a new behavioral procedure to investigate conditioned responding elicited by discrete appetitive cues

Authors: *M. D. VALYEAR[1], F. LACROIX[2], M.-P. COSSETTE[2], I. TRUJILLO-PISANTY[2], J.-M. MADDUX[2], P. SHIZGAL[2], N. CHAUDHRI[2];
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Abstract: Discrete and contextual Pavlovian cues that predict appetitive reinforcers influence the vigour with which those reinforcers are pursued. We assessed the role of dopamine in responding to discrete appetitive cues for sucrose and alcohol in isolation from contextual cues that predict the same unconditioned stimulus. Male, Long-Evans rats received 15% ethanol

(EtOH) in the home-cage, followed by Pavlovian conditioning sessions where a 10 s auditory conditioned stimulus (CS+; white noise or clicker; 15 trials/session) was paired with EtOH (0.2 ml/CS+, 3 ml/session). Conditioning sessions occurred on alternate days in a distinct Alcohol context where EtOH was dispensed into a fluid port during each CS+ trial. Entries into the port during the CS+ and 10 s preceding the CS+ (PreCS+) intervals were recorded. On intervening days rats were exposed to a different NonAlcohol context where a neutral and distinct auditory stimulus was played (15 trials/session) but EtOH was never delivered. After an equal number of sessions in both contexts, the CS+ was presented without EtOH in the Alcohol and NonAlcohol contexts to test alcohol-seeking behaviour elicited by the CS+. At test, rats made more port entries during the CS+ in the Alcohol context than in the NonAlcohol context. This contextually invigorated CS+ responding persisted across several subsequent EtOH-free test sessions. In addition, we found that dopamine D2 (Eticlopride, 10 µg/kg sc), but not D1 (SCH23390, 10 µg/kg sc), receptor antagonism attenuated CS+ responding in the NonAlcohol context. In a subsequent experiment we used this same conditioning paradigm with 10% sucrose to test the necessity of VTA dopamine neurons in responding to a discrete sucrose cue. Male transgenic TH::Cre rats received intra-VTA infusions of a cre-dependent viral vector encoding the Gi-Coupled (hM4Di) designer receptor. The hM4Di receptor induces neuronal silencing when bound by clozapine-n-oxide (CNO). After training the CS+ was played in the NonSucrose context following a systemic injection of vehicle or CNO (10 mg/kg ip). Results suggest that silencing VTA dopamine neurons dampens CS+ responding. Currently, chemogenetic inactivation of VTA dopamine neurons during alcohol seeking is being investigated. The studies herein demonstrate that the combination of discrete and contextual cues can robustly and persistently invigorate reward-seeking behaviour and that responding to discrete cues requires dopamine D2 receptors. Moreover, chemogenetics shows promise for uncovering the neural substrates of contextually-invigorated and context-independent reward seeking behaviour.

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Poster

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Title: Social reward valuation in primate midbrain dopamine cells

Authors: *A. NORITAKE[1], M. ISODA[2];
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Abstract: The ecological constrains inevitably lead living organisms to competition against others for a given resource (e.g., food, water, territory). Thus, one would devalue a context in which others acquire a reward more often, even though one's own chances of getting a reward may eventually be unchanged. It remains unclear what neural mechanisms underlie such subjective reward valuation via taking others' reward into account. To address this issue, we devised a social Pavlovian conditioning procedure using two monkeys (M1 and M2) facing each other. In the procedure, a visual conditioned stimulus (CS) differently signaled each monkey's reward probability and the monkeys were alternately conditioned in two contextually different trial blocks. In one block, the probability of a reward for M1 was the same, while that for M2 was variable. In the other block, the probability of M2's reward was constant, while the probability of M1's reward was variable. We previously demonstrated that the monkeys lowered the value of their own reward as their opponent's reward probability increased (SfN2014; 364.09). We also showed that distinct cell groups in the dorsomedial prefrontal cortex (DMPFC), a critical node in social brain networks, coded self-reward probability only, other-reward probability only, and subjective reward value in response to the CS (SfN2014; 364.10). However, what brain regions can provide neural substrates for such behavior and a variety of reward signals in the DMPFC remains elusive. A good candidate is the substantia nigra pars compacta and ventral tegmental area in which dopamine (DA) cells are located. While DA cells play a crucial role in self-reward processing and reward-based learning, it is still unexplored how they may code other-reward information. We recorded single-unit activity of 125 putative DA cells and analyzed their phasic responses to CSs (151 - 450 ms). The great majority of the cells (n=90) showed monotonically increasing activity as self-reward probability increased ($P < 0.01$). Among them, one-third (n = 35) also showed monotonically decreasing activity with increasing other-reward probability ($P < 0.01$), suggesting that they encoded subjective reward value. However, we did not find DA cells that selectively coded other-reward probability or those cells that coded reward saliency regardless of which monkey was to be rewarded. These results point to an integral role for DA cells in signaling subjective value on the basis of other-reward information and self-reward information in a manner consistent with reward prediction error coding. The DA cells may constitute a neuronal network for processing multiple reward signals in social contexts.

Disclosures: A. Noritake: None. **M. Isoda:** None.

Poster

636. Motivation and Emotion: Reward II

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Topic: F.03. Motivation and Emotion

Support: National Basic Research Program of China 2010CB833904

Title: Reward amplifies Simon effect by increasing the automatic activation of spatial code

Authors: *L. WANG, K. JIANG, S. LI, X. ZHOU;
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Abstract: Previous studies have shown that reward modulates conflict processing. However, it remains unclear whether and how reward modulates conflict processing at the response level. In the current study, we addressed this issue by investigating the neural mechanism of how reward affects the Simon effect, where response to a target in space is slowed down when the task-irrelevant stimulus location does not correspond to the response location. According to the well accepted dual-process model, the Simon effect arises from the conflict between the automatic activation of the stimulus location and the location of the response hand. In this study, we associated high or low reward with odd or even digits, which corresponded to left or right hand response, and we presented these digits at the location either congruent or incongruent with the location of response hand. We also recorded the event-related potential (ERP) components of lateral readiness potential (LRP) and N2pc. Behavioral results showed that the magnitude of Simon effect was larger for the high-reward digit than for the low-reward digit. ERP results showed that reward modulated the onset of the stimulus-locked LRP (sLRP), which reflects the automatic activation of the spatial code, but not the response-locked LRP (rLRP), which reflects the response execution process. Specifically, the difference in sLRP onset between the congruent and incongruent conditions was reduced for the high-reward digits as compared with the difference for the low-reward digits. Moreover, relative to the low-reward digits, the high-reward digits had enhanced amplitude of N2pc only in the congruent condition, not in the incongruent condition. The latency of N2pc was not modulated by reward, demonstrating more attention to but not earlier attentional processing of the reward-associated stimuli. Taken together, these results suggest that reward amplifies response conflict in Simon task by increasing the automatic activation of spatial code.

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Poster

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Topic: F.03. Motivation and Emotion

Support: Swedish Research Council (grant 2011-1529)

Marcus och Amalia Wallenbergs Minnesfond to IC (MAW 2014.0009)

Title: Neural correlates of touch reward

Authors: *C. TRISCOLI[1], G. HÄGGBLAD[2], H. OLAUSSON[4], I. CROY[5], U. SAILER[3]; [1]Dept. of Clin. Neurophysiology, Inst. of Neurosci. and Physiol., [2]Dept. of Pedagogical, Curricular and Professional studies, [3]Dept. of Psychology, Univ. of Gothenburg, Gothenburg, Sweden; [4]Dept. of Clin. and Exptl. Med., Univ. of Linköping, Linköping, Sweden; [5]Clin. for Psychosomatic Med., Tech. Univ. of Dresden, Dresden, Germany

Abstract: Introduction. Pleasant touch plays an important role in individuals´ subjective well-being and is assumed to form the basis for affiliative behaviour and social bonding. However, how long-lasting touch is processed by the brain's reward system is not understood yet. The aim of this study was to investigate how pleasant touch evolves over a long period of time and to determine neural activation in response to it. Methods. 25 subjects were scanned during 18 blocks of 2 minutes duration each. The first and the last block constituted a baseline. During the remaining 16 blocks in-between the subjects' left dorsal forearm was continuously stroked by a custom-built MR-compatible robotic device at a velocity of 3 cm/s for an average duration of 39 minutes. Subjective ratings of pleasantness were collected in-between the stroking blocks. Regions of interest in tactile areas (S1, S2 and posterior insula) and reward areas (orbitofrontal cortex, nucleus accumbens, putamen and caudate) were defined for the subsequent analysis. Results. Touch across all 16 stroking blocks compared to baseline showed activation in all tactile and reward ROIs. Enhanced activation in reward areas occurred in the last compared to the first stroking blocks. Conversely, enhanced tactile activation in the contralateral somatosensory cortices was shown at the first compared to the last stroking block. Activation in posterior insula remained constant. This was in parallel with increased functional connectivity of posterior insula with cingulate and striatal regions. Subjective ratings of pleasantness were related to activation in the orbitofrontal region. Discussion. Increased activation in reward areas was opposed by decreased activation in somatosensory tactile areas over time, with the influence of the posterior insula as mediator between these areas. Underlying mechanisms for increased activation in reward areas may involve a compensatory sensory habituation, potentially resulting while

experiencing a relevant and pleasant long-lasting stroking stimulation. This may promote seeking of long-term stroking and, consequently, social bonding.

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Poster

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Support: NIH 1ZIAMH002784

Title: Inhibition of adult hippocampal neurogenesis impairs motivation to obtain sucrose, but not food, reward using a progressive ratio responding paradigm

Authors: R.-M. KARLSSON, *H. A. CAMERON;
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Abstract: Inability to experience pleasure in normally pleasurable acts, anhedonia, is a characteristic seen in many psychiatric disorders including major depression, but is poorly understood. Previously our laboratory has shown that mice lacking neurogenesis show a depression-like phenotype including a decreased sucrose preference, which is a standard measure for studying anhedonia in rodents. The aim of the present study was to further investigate the role of adult hippocampal neurogenesis in motivation to obtain either sucrose or a food reward. We inhibited adult neurogenesis using valganciclovir in transgenic mice and rats that express herpes simplex virus thymidine kinase (TK) under the control of the GFAP promoter. Mildly food restricted TK and wild-type (WT) littermate controls were trained to lever press for either chocolate flavored sucrose tablets or regular food tablets on fixed ratio (FR) and exponentially progressive ratio (PR) tasks. Both TK mice and TK rats showed normal acquisition of lever press on a FR schedule and minimal pressing of inactive lever, suggesting normal learning of lever-reward association. When switched to a PR schedule, both mice and rats lacking adult neurogenesis showed significantly reduced responding compared to their WT controls when working for sucrose rewards. However, when working for food tablets, there was no difference between WT and TK in either acquisition or PR responding suggesting normal motivation to obtain a novel food reward. This study indicates that adult hippocampal neurogenesis affects motivation for some pleasurable/hedonic reward that is distinct from motivation for non-sweet

reward. Future studies will be needed to understand how new neurons in the hippocampus differentially affect motivation to consume sweet and non-sweet rewards.

Disclosures: R. Karlsson: None. **H.A. Cameron:** None.

Poster

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Title: Persistence of the effects of binge eating induction with corn oil in rats

Authors: *W. ZEPEDA-RUIZ[1], C. Y. RAMOS-LAZZARI[2], D. N. VELAZQUEZ-MARTINEZ[2];
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Abstract: Binge eating is characterized by overconsumption of food in brief periods in absence of an energy deficit. There are different animal models to study this disorder, one of them is the Limited Access which reproduces the overconsumption of palatable food in brief periods of time. It has been described that binge eating behavior induced with vegetable shortening or sucrose can persist for several months. We also found that binge eating can be induced with a 30% corn oil concentration; here, we describe the persistence of binge eating behavior induced with this palatable food. Twenty-four rats were divided in two groups: a) Control group and b) Experimental group; both groups had ad libitum access to food and water, control group had access to corn oil 24 hours seven days a week and experimental group had access for two hours on Tuesday, Thursday and Saturday. After one month of binge eating establishment, corn oil consumption was determined in both groups under the binge protocol. Test sessions were carried out in two different food conditions (ad libitum and deprivation). Corn oil consumption of the binge group remained at the same level for at least two months. Access to corn oil in the control group was allowed only on the test days and we found that their consumption increased; this increase may be related to the deprivation of corn oil during the days preceding the test. When both groups were chow deprived, differences in oil consumption vanished since the formerly control group increased their oil intake indicating that after experiencing high caloric food, they chose such food to replenish caloric content.

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Poster

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Title: Motivational state but not reward value or Pavlovian cues affect forelimb motor skill learning in rats

Authors: ***A. C. MOSBERGER**, L. DE CLAUSER, H. KASPER, M. WIECKHORST, M. E. SCHWAB;
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Abstract: Motor skill learning as well as the recovery of skilled movements after central nervous system (CNS) injuries is widely studied in rodents with the skilled grasping task. By using direct food reward in the form of sugar pellets, this task contains an inherent motivational component. The role of motivation in motor learning is often studied in human subjects and its role in rehabilitation success is a well-known phenomenon amongst physiotherapists. However, a connection to the most commonly used animal model and task is still missing. In the current study, we evaluate the role of motivation in learning and plateau performance of an instrumental skilled grasping task in rats. In this task, animals have to perform a chain of actions to retrieve a sugar pellet from a pedestal. To initiate a trial, the animal activates a nose poke sensor (action 1, distal to reward) to open a motorized door, giving access to the pedestal. The animal then approaches the pedestal and uses its forelimb to reach for and grasp the sugar pellet reward (action 2, proximal to reward). Completion of this movement ends the trial and the motorized door closes again. In the first experiment, we used food rewards of differentially preferred flavors (reward value) and found no effect on skilled grasping learning and performance (action 2), or on nose poke response behavior (action 1). In the second experiment, Pavlovian incentive learning was used to motivate the performance of the instrumental skilled grasping task.

Although we found a strong effect on approach behavior towards the reward, there was no effect of the Pavlovian cue on skilled grasping learning and performance (action 2), or on nose poke response behavior (action 1). In the third experiment, we changed the animals' motivational state by using different levels of food deprivation and found a strong effect on both, the distal nose poke response (action 1) and the skilled grasping learning and performance (action 2). These experiments suggest that motivational manipulations can have differential effects on specific components of an instrumental skilled motor task. These findings have implications for the design and use of such a task in the study of motor learning and recovery after CNS injury.

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Poster

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NARSAD Young Investigator Award to WKS

Title: Resting-state functional connectivity between interoceptive cortex and reward circuitry modulates ratings of inferred food pleasantness

Authors: *K. BURROWS[1], J. A. AVERY[1], K. L. KERR[1,2], C. MULLINS[1], J. BODURKA[1,4], W. K. SIMMONS[1,3];
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Abstract: Although increased or decreased appetite are common symptoms during acute episodes of major depressive disorder (MDD), the neural bases for these MDD-associated appetite changes remain poorly understood. Two recent fMRI findings have revealed interesting insights. First, appetite increase in MDD is associated with increased brain activity in putative reward neurocircuitry to the sight of food, while MDD-related appetite loss is associated with decreased activity in a region of the dorsal mid-insula known to underlie interoceptive signaling. Second, those depressed individuals with appetite increases who rate visually perceived foods as being most appealing also exhibit the weakest activity in interoceptive cortex during food

perception. These findings suggest that food value decisions arise from interactions between interoceptive and reward circuitry. If so, we hypothesize that food value judgments should be related to the intrinsic functional connectivity between interoceptive and reward neurocircuitry. To test this hypothesis, we recruited two groups of participants with MDD, one with increased appetite and one with decreased appetite, as well as non-depressed adults. Participants completed an 8-minute resting-state fMRI scan, followed by a food pleasantness task in which they made hedonic inferences about appetizing foods depicted in photographs. To assess functional connectivity, a region of the right dorsal mid-insula was selected as a seed region. Notably this region of the insula has been previously identified as responsive in healthy subjects to pictures of foods and interoceptive awareness of visceral signals. At the group level, the average ratings from the food pleasantness task were regressed on to the subjects' insula resting-state functional connectivity maps, and the resulting statistical images were corrected for multiple comparisons at $p<0.05$. We found that subjects' food pleasantness ratings were positively correlated with the resting-state functional connectivity between the dorsal mid-insula (interoceptive cortex) and reward-related regions of the brain, including the accumbens area and a region of the ventromedial prefrontal cortex associated with food value estimation. Interestingly individuals who exhibited the strongest functional connectivity between interoceptive and reward brain regions later expected foods to be more pleasant. This finding reveals important insight into how the brain predicts food hedonic value through the synchronization of reward and interoceptive neurocircuitry.

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Poster

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Title: Examination of the addictive properities of the anandamide transport inhibitor SBFI26

Authors: *P. K. THANOS[1], B. CLAVIN[1], J. HAMILTON[1], J. O'ROURKE[1], T. MAHER[1], C. KOUMAS[1], E. MIAO[1], A. ELHAGE[1], G. TENG[2], M. KACZOCHA[3], D. DEUTCH[4]; [1]Psychology, [2]Chem., [3]Anesthesiol., [4]Biochem., Stony Brook Univ., Stony Brook, NY

Abstract: The therapeutic properties of cannabinoids have been well demonstrated but are overshadowed by such adverse effects as cognitive and motor dysfunction as well as their potential for addiction. Recent research on the natural lipid ligands of CB1 receptors, also known as endocannabinoids, have shed light on the mechanisms of intracellular transport of the endocannabinoid anandamide by fatty acid binding proteins (FABPs) and subsequent catabolism by fatty acid amide hydrolase (FAAH). These findings facilitated the development of SBFI26 (Berger et al. 2012), a pharmacological inhibitor of brain-specific FABP5 and FABP7, which effectively elevates extracellular concentrations of anandamide. The goal of this study was to examine this compound for any possible effects on reward and addictive properties as well as locomotor effects given its recently reported anti-inflammatory and analgesic properties. Mice were separated into one of four treatment groups [vehicle or SBFI26 (5, 20, 40 mg/kg)]. After a habituation session, mice underwent an 8-day conditioning phase before testing. Treatment was given 1 hour prior to being placed in a conditioned place preference (CPP) apparatus. Preference was determined based on percentage of total time spent in each chamber. In addition, mice were also tested for locomotor activity as measured in an open field arena. Results showed that mice treated with SBFI26 did not show conditioned placed preference (CPP), nor conditioned place aversion. In addition, SBFI26 did not show any effect on locomotor activity during CPP or following acute treatment in an open field activity. In conclusion, these findings suggest that SBFI26 did not show addictive properties - as measured by CPP, nor did it produce any effects on locomotor activity. Therefore, FABP inhibition may provide therapeutic potential for analgesia and inflammation without the risk of dependence or motor impairment.

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Poster

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Support: NIMH R01 MH082017

Title: Representation of social hierarchy and fluid value in the primate amygdala

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Abstract: Primates are social animals, and they live in groups. Group living can help individuals defend against predators and acquire nutrition, among other functions. Within a group of primates, however, conflicts between group members can arise (food sharing, mating, etc.), requiring individuals to know the status (i.e. the social position) of each group member to promote survival. Presumably monkeys learn the social status of group members through experience, just like they learn the rewarding or aversive nature of sensory stimuli that predict different types of reinforcement. Group members may thereby be viewed as differing in value. We sought to understand how the brain represents the status of each member within a social hierarchy. We hypothesized that neural representations of social hierarchy emerge in the same neuronal populations engaged in reinforcement learning and the assignment of motivational significance to previously neutral stimuli. Our initial target for study was the primate amygdala, since it has been implicated in the processing of social stimuli and of stimuli associated with rewarding and aversive events. Actor monkeys performed two types of blocks of a trace conditioning task. In one type, monkeys viewed a fractal image (conditioned stimulus, CS) that could be associated with 3 different rewards (2, 1 or 0 drops of juice delivered after a trace epoch). In the second block type, CSs were pictures of monkeys belonging to the actor monkey's group ; all completed trials resulted in delivery of one drop of juice. We computed a social index based on the trial completion rate, the type of error made, and the viewing times of different features of the images. The computed social index was similar to the social hierarchy observed between the members of the group by independent observers (e.g. the Alpha monkey of the group was the one with the highest index). We computed an analogous index for the fractal image blocks, and found a similar trend as for the social blocks: high, medium and small index values for large, medium and no reward CSs respectively, raising the possibility that the social and fluid index values reflect actor monkey preferences. Preliminary neurophysiological data reveal that the same population of neurons in the amygdala can be used to decode the reward value of CSs and the social hierarchy of the group. These results suggest a common neural substrate for processing motivationally significant social and non-social stimuli. The acquisition of neural representations of social hierarchy may therefore arise in the same neural circuits that link representations of non-social sensory stimuli with innately rewarding or aversive reinforcement.

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NCATS CTSA UL1 TR000142

Title: Linking neural patterns and behavioral models of outcome anticipation through representational similarity analysis

Authors: D. B. EHRLICH[1,2], Z. ZHANG[1,2], *I. LEVY[1,3,2];
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Abstract: Imaging studies of reward anticipation have in the past found it difficult to adequately differentiate signals representing value and salience due to their partially confounding relationship. In combination with careful experimental design, one way to begin to examine these competing representations is through multivariate analysis methods, which are capable of deciphering more complex representational patterns in the brain compared to univariate techniques. While such multivariate methods, most notably Multi-Voxel Pattern Analysis (MVPA), have made strides in identifying subtle spatiotemporal encoding patterns, they often deliver results that are impenetrable to further interpretation. Representational Similarity Analysis (RSA; Nili et al, 2014), a novel and less widely utilized multivariate method, enables complex non-linear pattern recognition, while presenting results in an intuitive form directly comparable to computational models and behavioral data. RSA relies on mapping condition-by-condition similarities in neural data, which can then be compared to competing models of stimuli or behavioral similarity across the same set of conditions. In our study, RSA was used to compare similarity in prefrontal cortex (PFC) activation patterns, as we systematically varied saliency and value between conditions. 18 healthy subjects were scanned as they participated in a reward and punishment task. On each trial, participants were presented with probabilistic reward and punishment cues, drawn from 4 categories (money gains, money losses, pleasant pictures and shocks) each with 4 intensity levels. RSA demonstrated that neither a model drawn from subject pleasantness ratings, nor one based on inferred saliency strongly predicted the observed neural conditional similarity. A model integrating the two signals, however, in which saliency played a modulatory role in representational consistency both strongly matched the observed PFC activity as well as far outperformed the two other behavioral models. By modeling the full set of experimental conditions, while accounting for consistent patterns in voxel-by-voxel information, RSA provides a powerful method for exploring the underlying representation in

complex activation patterns. In further analysis we will use RSA to examine theories of common value and uncertainty representations across domains as well as begin to isolate theories of subjective value construction, integration, normalization and comparison that maximize biological and representational plausibility.

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Poster

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Title: Propranolol interferes with the reconsolidation of a sign-tracking, but not a goal-tracking conditioned response

Authors: *E. S. COGAN, N. C. TRONSON, T. E. ROBINSON;
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Abstract: In Pavlovian conditioning, individuals vary in the extent to which they approach and interact with the cues in their environment. Upon presentation of a lever conditioned stimulus (CS), some animals will vigorously interact with it and approach it (sign-trackers-ST), while others will approach the location of the reward delivery (goal-trackers-GT). However, when using a tone CS, animals cannot interact with it or approach it, thus forcing all animals to exhibit a goal-tracking conditioned response. Previous studies have examined the neurobiological mechanisms required for the expression of these phenotypes using both a lever and tone CS; however, the mechanisms underlying reconsolidation of lever and tone CS-US memories in STs and GTs have not yet been studied. In the present study, we utilize these individual differences in autoshaping to examine the effect of systemic injections of beta adrenergic receptor antagonist, propranolol on ST and GT behavior to a lever and tone CS. In experiment 1, animals were first classified as STs or GTs in a lever autoshaping task previously described followed by two successive days of autoshaping sessions in which rats were administered a post-session intraperitoneal injection of either propranolol (20 mg/kg) or saline. Animals underwent autoshaping for an additional day to assess behavior following the second injection day. We found that propranolol decreased ST behavior in STs, but not GT behavior in GTs, relative to saline controls. In experiment 2, the procedure was identical with the exception that a tone CS

was used. Under these conditions, GT behavior was again unaffected by propranolol. Propranolol has been previously reported to disrupt the reconsolidation of emotional memories in both appetitive and aversive learning. The present study suggests norepinephrine (NE) is required for reconsolidating ST memories. Additionally, it suggests that the psychological processes of ST and GT behavior may be fundamentally different in that ST is an emotional process, while GT is not.

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Poster

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Title: Oxytocin and playfulness in juvenile Fischer 344 and Lewis rats

Authors: *S. M. SIVIY, C. C. GARLISS, L. S. MCDOWELL, S. R. ECK, J. A. SOROKA; Dept Psychol, Gettysburg Col., Gettysburg, PA

Abstract: Oxytocin (OT) modulates a wide range of mammalian social behaviors, yet relatively little is known about the role of this neuropeptide in the control of playfulness. Previous work from our laboratory has shown that the Fischer 344 (F344) rat is consistently less playful than other inbred and outbred strains and we have been investigating (1) whether some of the strain differences in playfulness may be associated with systematic differences in OT functioning and (2) whether OT may have a modulatory influence over playfulness in juvenile rats, including the relatively non-playful F344 rat. We have previously observed a modest strain difference in hypothalamic OT, with F344 rats having fewer OT-positive neurons in the paraventricular nucleus of the hypothalamus (PVN) than male SD rats. We expanded on this earlier study to include males and females, as well as the inbred Lewis rat. Slices were taken through the hypothalamus of juvenile male and female F344, SD, and Lewis rats and processed immunohistochemically for OT-positive neurons in the PVN. No differences were found between SD and F344 rats for total number of OT-positive neurons, while male and female Lewis rats had significantly fewer OT-positive neurons than either SD ($p = .01$) or F344 ($p = .05$) rats. When adjusted for PVN volume of the sampled sections, Lewis females continued to show fewer OT-positive neurons than all other groups. While these data reinforce strain differences in

the number of OT neurons in the PVN, the observed differences were not as predicted and cannot readily account for strain differences in playfulness. We have also begun to assess the effects of intracranial infusions of OT into limbic structures thought to be involved in play and that have abundant OT receptors. Bilateral infusions of OT (1 μg/0.5 μl) or saline were made into the central amygdala of male and female F344 and Lewis rats immediately before being paired with an un-treated SD rat for 10 minutes. Play was quantified primarily by the frequency of pounces directed towards the SD partner. OT significantly increased pouncing in both male F344 and Lewis rats, while having minimal effects on females. OT has been shown by others to result in excessive grooming when infused into the central amygdala and we also observed substantial OT-induced self-grooming (> 600% over saline). The magnitude of grooming was strongly correlated with increased pouncing ($r = 0.79$, $p = .004$), suggesting a shared substrate for both effects. These data suggest that while compromised OT functioning may not contribute to the dysfunctional play of F344 rats, OT acting within the central amygdala may be an important modulator of playfulness in juvenile rats.

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WHEELER CENTER FOR THE NEUROBIOLOGY OF ADDICTION

Title: Behavioral responding in the discriminative stimulus task is habitual

Authors: *J. MEFFRE[1,2], H. FIELDS[2], F. AMBROGGI[1,2];
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Abstract: The nucleus accumbens core (NAc) is essential in cue-controlled reward-seeking such as in the discriminative stimulus (DS) task. In this task, NAc inactivation reduces operant responding to the DS. We previously showed which input signals are necessary for the NAc to drive behavioral responding. However, these studies did not allow to determine which

underlying cognitive process was used in the DS task. In particular, it is essential to determine whether rats use a representation of the outcome to guide reward-seeking. If the animal uses a representation of the outcome, the behavior is said goal-directed and can be adapted flexibly according to the motivational state. Habitual responding on the other hand does not depend on such representation and is driven systematically by the presentation of the stimulus. To test whether the DS task is goal-directed or habitual, we used a standard lithium chloride devaluation procedure. In the DS task, one of two distinct auditory cues, a DS and a neutral stimulus (NS) is presented every of 30 sec to food-restricted rats. The DS predicts a liquid sucrose reward if the animal presses a lever within 10 sec. Responding to the NS has no consequence. After being trained to the task, rats were split in two groups. The devaluated group received 5 LiCl injections every other day immediately after a 20 minute-free access to the sucrose reward. The non-devaluated group received free access to sucrose and LiCl injections on alternate days. When instrumental performance in the DS task was then tested in extinction, both groups continued to press the lever associated with the DS at the same rate than during training. When rats were tested in the rewarded DS task the following day, performance was also equivalent between devaluated and non-devaluated groups. These results suggest that sucrose seeking in the DS task is a habit rather than a goal-directed behavior and therefore implicate the NAc as a locus of control of stimulus-response behaviors.

Disclosures: **J. Meffre:** None. **H. Fields:** None. **F. Ambroggi:** None.

Poster

636. Motivation and Emotion: Reward II

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 636.18/DD24

Topic: F.03. Motivation and Emotion

Support: National Science Foundation Graduate Research Fellowship DGE-1122492

NIMH grant K01MH099232

Title: The neural correlates of dynamic goal pursuit

Authors: ***K. M. ANDERSON**, L. M. PATRICK, J. REINEN, A. J. HOLMES;
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Abstract: The ability to pursue goals through an ever shifting and uncertain environment is core to human survival. To accomplish this, the brain must integrate internal and external stimuli

across multiple time scales. Prior work based on descriptions of discrete moments during reward anticipation and consumption has greatly advanced understanding of the cortico-striatal circuits that support motivated behavior. Yet relatively little is known about the dynamic neural mechanisms that underlie sustained goal pursuit in humans. Recent work in rodents identifies a 'ramping' of ventral striatal neural activity and dopamine release linked to the spatial proximity of an expected reward (Howe et al., 2013; van der Meer and Redish, 2011). However, the dynamic ramping of ventral striatal activity in response to the spatial proximity of anticipated outcomes has yet to be established in humans. Further, the potential links between this signal and the function of large-scale cortical networks remain an open question. In the present ongoing study, participants underwent functional MRI (fMRI) while navigating through a virtual reality T-maze. At the onset of each trial, a cue was presented predicting the value and probabilistic location of a monetary reward. Participants utilized the cue to predict reward location. Participants then manually navigated through the maze to their selected arm, where they were provided feedback. Although the current design is more complex than traditional tasks, analyses reveal canonical neural activity in the ventral striatum and medial prefrontal cortex in response to reward cues and outcomes. Ongoing timecourse analyses aim to identify neural signals that associate with reward proximity. fMRI data will be analyzed for ramp-like signals that are modulated by reward level (i.e. $0, $1, or $5) and by maze length (i.e. short or long T-maze). By revealing how dynamic goal monitoring is instantiated in the brain, the current study can inform how motivated behavior is directed and maintained over time.

Disclosures: K.M. Anderson: None. **L.M. Patrick:** None. **J. Reinen:** None. **A.J. Holmes:** None.

Poster

636. Motivation and Emotion: Reward II

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Topic: F.03. Motivation and Emotion

Support: NRSA 1F32DA038942

TNDA 5T32DA024635

R01-DA035443

Title: Glutamate released into the basolateral amygdala tracks the encoding of reward value and the use of this information to guide reward seeking

Authors: *M. MALVAEZ[1], S. STOLL[1], A. M. YORITA[2], L. FENG[2], H. G. MONBOUQUETTE[2], K. M. WASSUM[1];
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Abstract: Reward-seeking decisions are heavily controlled by the incentive value (i.e., desirability) of the specific reward they attain. This value is acquired and updated through the process of instrumental incentive learning, during direct experience of the specific reward in a relevant motivational state. Although the basolateral amygdala (BLA) has been generally implicated in the encoding and use of reward value information to guide decisions, almost nothing is known about the neurotransmitter processes within this structure mediating these effects. The BLA is densely innervated by both cortical and thalamic glutamatergic projections, so we hypothesized that glutamate released into the BLA would track changes in reward value important for value-guided decisions. To test this we used electroenzymatic biosensors to make near-real time measurements of BLA glutamate concentration changes during an incentive learning experience and during the subsequent use of this updated reward representation to guide reward-seeking decisions. Rats were trained mildly food-deprived to lever press for a food reward. When rats were then allowed to experience the food reward hungry for the first time, we found that BLA glutamate concentration was transiently elevated and that this signal tracked the incentive learning process. Glutamate elevations were not detected in a control group of subjects when they experienced the food reward in the familiar, mildly food-deprived control state. The next day all rats were tested hungry for their reward-seeking activity. Excitingly, we detected transient fluctuations in BLA glutamate concentration immediately preceding reward-seeking actions, but only in those rats who had been given the opportunity to learn the food reward's higher value when hungry. These data suggest transient BLA glutamate release tracks the reward evaluation process that drives value-based reward seeking decisions and perhaps also the use of this value information to guide reward-seeking decisions.

Disclosures: M. Malvaez: None. **S. Stoll:** None. **A.M. Yorita:** None. **L. Feng:** None. **H.G. Monbouquette:** None. **K.M. Wassum:** None.

Poster

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Support: China MOST 2012CB837701

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NNSFC 91432114

Beijing Municipal Government

Title: Cell-type specific responses to reward and punishment in the dorsal raphe of freely behaving mice

Authors: *Y. LI[1,2], W. ZHONG[1,2], D. WANG[1,3], J. ZHOU[1,4], F. HU[1], Z. LIU[1], Q. FENG[1], C. JIA[1], J. ZENG[1], Q. GUO[1,5], M. LUO[1,3];
[1]Natl. Inst. of Biol. Sciences, Beijing, Beijing, China; [2]Grad. Sch. of Peking Union Med. Col., Beijing, China; [3]Sch. of Life Sciences, Tsinghua Univ., Beijing, China; [4]PTN Grad. Program, Sch. of Life Sciences, Peking Univ., Beijing, China; [5]Britton Chance Ctr. for Biomed. Photonics, Wuhan Natl. Lab. for Optoelectronics-Huazhong Univ. of Sci. and Technol., Wuhan, China

Abstract: The dorsal raphe nucleus (DRN) appears to process signals that concern reward and punishment; however, it remains unclear how 5-HT neurons and GABA neurons in the DRN respond when freely behaving animals perform reward-associated behaviors. Here, we addressed this question using fiber photometry and single-unit recording from genetically defined neurons in the mouse DRN. Natural rewards (sucrose and food) strongly activated 5-HT neurons, but aversive stimuli (quinine and footshock) did not. After a mouse learned to wait for delayed sucrose delivery, most 5-HT neurons fired tonically during waiting and then phasically upon reward acquisition, although a minority of 5-HT neurons showed different response profiles. Finally, the activity of GABA neurons was suppressed during animal reward seeking. Thus, DRN 5-HT neurons and GABA neurons encode reward signals via excitation and inhibition, respectively, suggesting their roles in mediating both anticipatory and consummatory responses to rewards.

Disclosures: Y. Li: None. **W. Zhong:** None. **D. Wang:** None. **J. Zhou:** None. **F. Hu:** None. **Z. Liu:** None. **Q. Feng:** None. **C. Jia:** None. **J. Zeng:** None. **Q. Guo:** None. **M. Luo:** None.

Poster

636. Motivation and Emotion: Reward II

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Topic: F.03. Motivation and Emotion

Support: Grant-in-Aid for Young Scientists (B)

Grant-in-Aid for JSPS Fellows

Title: Pupil dynamics represent human task performance prior to the execution

Authors: *N. WATANABE[1,2,3,4], H. OHIRA[1];
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Abstract: Avoiding negative outcomes and maximizing rewards are goals common to most individuals. However in reality, we sometimes fail to achieve these goals because of difficulty in regulating emotions caused by external stress or internal spontaneous state. It suggests that human brain modulates his/her inner arousal level to successfully complete challenging task. In this study, we monitored subjective arousal levels with pupil dynamics of eyes when the participants engaged in the challenging task (Stop watch task: n = 24). They were required to stop the watch at exactly five seconds without seeing the counting display. If they could stop the watch prescribed duration (e.g. 4.8~5.2 sec.), they could earn some monetary rewards which represented as the cue timing (10~990 yen for each trial) before the execution. As results, step-wised multiple regression analysis showed that the pupil dynamics at the ready timing (in 5.5 sec.) prior to the counting the numbers in their head significantly represented the interaction (performance & reward size) (Mean $\beta = -0.0531 \pm 0.0001$, $ps < 0.05$) as well as main effect of reward size (Mean $\beta = 0.1121 \pm 0.0002$, $ps < 0.05$) from approximately 1.5 to 5.5 sec. Further analyses in this interval showed that although the pupil dynamics were strongly affected by the reward size in the case of lowest performances, they showed stable waveforms regardless of monetary size in the case of highest performances (Individual data fittings with linear functions; gradients: $F(2.399, 52.784) = 4.180$, $p = 0.015$). These data do not only indicate that the pupil dynamics represent the arousal level objectively, there is also a possibility that the performance for each trial could be predicted prior to the execution.

Disclosures: N. Watanabe: None. **H. Ohira:** None.

Poster

637. Sensory and Motor Systems in Invertebrates

Location: Hall A

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Topic: F.04. Neuroethology

Support: The University of Texas at Austin Undergraduate Research Award to CB

NIH NINDS grant NS075541 to JTP-S

Title: The magnetotactic response of *C. elegans* wild-type isolates displays adaptations across different geographical regions

Authors: *A. G. VIDAL-GADEA[1,2], C. BAINBRIDGE[1], C. C. BERON[2], K. WARD[2], N. GHORASHIAN[3], S. GOKCE[3], J. RUSSELL[2], N. TRUONG[2], A. PARIKH[2], O. PAPOULAS[4], D. BOUTZ[4], O. E. GADEA[2], E. MARCOTTE[4], A. BEN-YAKAR[3], J. T. PIERCE-SHIMOMURA[2];
[1]Sch. of Biol. Sci., Illinois State Univ., Normal, IL; [2]Neurosci., [3]Mechanical Engin. Dept., [4]Ctr. for Systems and Synthetic Biol., The Univ. of Texas at Austin, Austin, TX

Abstract: The magnetic field of the earth is a source of constant and reliable directional information for a vast number of organisms able to detect it. While some animals such as turtles and birds use the magnetic field to engage in horizontal migrations, other organisms like magnetotactic bacteria use it to guide their migrations vertically. The nematode *C. elegans* readily orients to artificial magnetic fields of earth strength. We found that worms appear to use the geomagnetic field to guide vertical migrations via an identified a pair of sensory neurons. Because the orientation of the geomagnetic field differs across the globe, we tested the magnetotactic ability and migratory preference of the standard lab strain (N2), and of wild-type strains isolated from different locations across the planet. We found that different populations displayed an innate preference to migrate at an angle to magnetic fields of earth-strength that would optimize their UP or DOWN direction when burrowing in their native global location. For instance, in England the geomagnetic field pierces the earth at +66 degrees (north points down). We found that well-fed British N2 worms prefer to migrate 120 degrees to an earth-strength artificial magnetic field. This seemingly arbitrary angle corresponds to the optimal angle to orient them upward when burrowing in England. By contrast, starved N2 worms migrated in the opposite direction (i.e. 300 degrees to the field), which would orient them downward in England. Consistent with natural populations adapting to local magnetic fields, we next found that worms isolated from Australia, where the geomagnetic field emanates out of the earth at -66 degrees (north points up), displayed an opposite innate pattern of migratory preference. Similar results were found for wild-type worms from Hawaii. This pattern of optimal natural variation in magnetic orientation in *C. elegans* serves as an excellent example to relate spatiotemporal genetic variation with a behavioral trait. The breath in number and distribution of wild-type *C. elegans* populations makes this a promising model for studying the effects of natural and artificial magnetic field variation on the behavior of a genetically tractable animal.

Disclosures: **A.G. Vidal-Gadea:** None. **C. Bainbridge:** None. **C.C. Beron:** None. **K. Ward:** None. **N. Ghorashian:** None. **S. Gokce:** None. **J. Russell:** None. **N. Truong:** None. **A. Parikh:**

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Poster

637. Sensory and Motor Systems in Invertebrates

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Topic: F.04. Neuroethology

Support: Dubner Fellowship

Alfred P. Sloan Foundation

University of Chicago Big Ideas Generator

Title: Investigating the neural basis of color-based mate choice preferences in Heliconius butterflies

Authors: *N. P. BUERKLE[1,2], E. WESTERMAN[3], M. R. KRONFORST[3], S. E. PALMER[1,2]; [1]Committee on Neurobio., [2]Dept. of Organismal Biol. and Anat., [3]Dept. of Ecology and Evolution, Univ. of Chicago, Chicago, IL

Abstract: Color based mate choice in an adaptive radiation of Heliconius butterflies is an attractive system for studying how nervous systems evolve to produce novel behaviors. Here, we focus on Heliconius cydno alithea and H.c. galanthus, a group of species where wing coloration is controlled by a single Mendelian locus, with white coloration dominant over yellow. Prior behavioral work has shown that male homozygotes preferentially court females of the same color independent of species identity, while heterozygotes show no preference. To differentiate between a change in peripheral sensory reception and a difference in central brain processing, we are characterizing the eyes of homozygote butterflies using intracellular photoreceptor recordings to construct tuning curves, eyeshine microscopy and histology to identify colored screening pigments that act as pre-neural light filters, and antibody staining to examine patterns of fruitless expression, a well-known marker of cells important for courtship. Preliminary results using electroretinogram recordings suggest that spectral tuning between the two species are not significantly different from each other or from the closely related red H. melpomene. Eyeshine data indicates that these butterflies have at least two types of screening pigments, which are mostly red with some yellow. Additionally, RNA-Seq data from the eye indicates fruitless transcripts are present in male eyes one day after eclosion. The results of this study will begin to

explain how genes affect behavior at the level of neural circuits and lead to a greater understanding of how neural computation can change within the constraints of evolution.

Disclosures: **N.P. Buerkle:** None. **E. Westerman:** None. **M.R. Kronforst:** None. **S.E. Palmer:** None.

Poster

637. Sensory and Motor Systems in Invertebrates

Location: Hall A

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Program#/Poster#: 637.03/DD30

Topic: F.04. Neuroethology

Support: NIMH

Title: Local structure of subcellular input retinotopy in an identified visual interneuron

Authors: ***Y. ZHU**, F. GABBIANI;
Dept. of Neurosci., Baylor Col. of Med., Houston, TX

Abstract: The Lobula Giant Movement Detector (LGMD) is an identified visual interneuron in the locust that responds preferentially to objects approaching on a collision course. The LGMD receives excitatory input from the entire visual hemifield sampled by one eye that appears to preserve retinotopy down to the level of single facets on the compound eye. Because single photon imaging with CCD sensors has a relatively low penetration and exhibits considerable scattering, previous work could not directly investigate this retinotopic mapping at the level of individual thin dendritic branches. Our current work employs a custom-built two-photon microscope with sub-micron resolution in conjunction with an OLED (Organic Light-Emitting Diode) microdisplay that provides visual stimuli to the locust compound eye adequate to explore this retinotopy at the finest level. We find that the adjacent facets on the compound eye have overlapped dendritic mappings on the LGMD excitatory dendritic branch. Furthermore, the centers of mass of the dendritic branches activated by individual single facets build a retinotopic map, consistent with earlier results obtained through CCD imaging. Different facets seem to make independent synaptic contacts onto the LGMD. The separation of center-of-masses along the dorsal-ventral axis is larger than along the anterior-posterior axis. Simultaneously stimulating 2 facets results in responses similar to the sum of responses from 2 single-facet stimuli. Flashed stimuli covering three concentric facet layers generate larger responses than stimuli expanding over the same area. Translational stimuli moving from anterior to posterior generate stronger responses than similar stimuli moving from posterior to anterior. Our work reveals several new

properties of the local structure of subcellular input retinotopy that will allow more detailed modeling of the LGMD in the future.

Disclosures: **Y. Zhu:** None. **F. Gabbiani:** None.

Poster

637. Sensory and Motor Systems in Invertebrates

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Program#/Poster#: 637.04/DD31

Topic: F.04. Neuroethology

Support: MEXT KAKENHI Grant Number 26440176

MEXT KAKENHI Grant Number 26119501

JST PRESTO

Title: Direction-specific adaptation in neuronal and behavioral responses of cercal sensory system in the cricket

Authors: ***H. OGAWA**[1], R. MITANI[2], K. OKA[3];
[1]Dept. of Biol. Sciences, Fac. of Sci., [2]Biosystem Sci. Course, Grad. Sch. of Life Sci., Hokkaido Univ., Sapporo, Japan; [3]Dept. of Biosci. and Informatics, Fac. of Sci. and Technol., Keio Univ., Yokohama, Japan

Abstract: Stimulus-specific adaptation (SSA) is considered as the neural underpinning of habituation to frequent stimuli and novelty detection. However, neither the cellular mechanism underlying SSA nor the link between SSA-like neuronal plasticity and behavioral modulation is well understood. Cricket wind-detection system is one of the most suited models for investigating the neural basis of SSA. We found that crickets exhibit stimulus direction-specific adaptation in wind-elicited avoidance behavior. Repetitive air currents inducing this behavioral adaptation reduced firing responses to the stimulus and amplitude of excitatory synaptic potentials (EPSPs) but did not modulate paired-pulse ratio of EPSPs in wind-sensitive giant interneurons (GIs) related to the avoidance behavior. Injection of Ca^{2+} chelator, BAPTA into GIs diminished both response attenuation and synaptic depression induced by the repetitive stimulation, suggesting that adaptation of GIs induced by the repetitive stimulation is Ca^{2+}-mediated short-term depression at sensory afferent-to-GI synapses. Some types of GIs showed adaptation specific to direction of repetitive stimuli, resulting in alternation of directional tuning curve. Optical imaging of dendritic Ca^{2+} responses revealed that a transient rise in Ca^{2+} was

restricted to the specific area of dendrites in the types of GIs of which directional tuning was altered. In contrast, other type of GIs with constant directionality exhibited global Ca^{2+} elevation throughout the dendritic arbor. These results suggest that depression induced by local Ca^{2+} accumulation at continually activated synapses of key neurons underlies direction-specific behavioral adaptation. This input-selective depression mediated by heterogeneous Ca^{2+} dynamics could confer animals with the ability to detect novelty at the earliest stages of sensory processing.

Disclosures: **H. Ogawa:** None. **R. Mitani:** None. **K. Oka:** None.

Poster

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Topic: F.04. Neuroethology

Support: MEXT KAKENHI Grant 26119501

MEXT KAKENHI Grant 26440176

Title: Preceding auditory inputs modulate responsiveness and orientation in wind-elicited walking behavior in the cricket

Authors: ***M. FUKUTOMI**[1], H. OGAWA[2];
[1]Grad. Sch. of Life Sci., [2]Dept. of Biol. Sci., Fac. of Sci., Hokkaido Univ., Sapporo, Japan

Abstract: Animals flexibly alter their movements depending on their environmental context or experiences even if they receive identical stimulus that trigger stereotypical behavior. The context-dependent changes in locomotion are also observed in escape behavior (Domenici, 2010). For example, the goldfish against the wall alters escape direction in response to auditory stimulus to avoid collision with wall (Eaton and Emberley, 1991). This means that additional sensory inputs in different modality affect on the neuronal circuitry directing the avoidance behavior. However, relationships between characteristics of the modulating stimulus and behavioral change remain unknown. To address this question, we adopted wind-elicited walking in the crickets as experimental model. Crickets exhibits the oriented escape walking response to short airflow stimulus (Oe and Ogawa, 2013), which is mediated by wind-sensitive organ called 'cerci' at the rear of the abdomen. The auditory stimulus detected by tympanal organ at frontal legs also elicites distinct oriented behaviors. Female crickets exhibit positive phonotaxis in

response to conspecific male's calling songs (Hedwig, 2006). In contrast, ultrasound produced by approaching bats induces negative phonotaxis in flying cricket (Moiseff et al., 1978). We have been reported that tone sound preceding air puff by 800 ms biased the walking direction backward and increased response threshold of the wind-elicited escape behavior (Fukutomi et al., 2014, SfN meeting). This auditory modulation was independent from on the coincidence in stimulus directions between tone and air puff. In this study, we examined these effects of the acoustic stimulus with various temporal characteristics on the wind-elicited walking. Simultaneous exposure of tone and air puff with no delay had no effect, but preceding tone but non-overlapped with air-puff stimulus also altered the walking direction. Furthermore, and tone preceding air puff by 200 ms increased turn angle in addition to modulation in direction and threshold. These results suggest that preceding auditory inputs produce different context for the cricket and modulate the cercal-mediated escape behavior.

Disclosures: **M. Fukutomi:** None. **H. Ogawa:** None.

Poster

637. Sensory and Motor Systems in Invertebrates

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Program#/Poster#: 637.06/DD33

Topic: F.04. Neuroethology

Support: Andrews University Undergraduate Research Scholar Award

Title: The effect of calling songs with multiple frequencies in the phonotactic response of female cricket Acheta domesticus

Authors: *J. MENDONCA, B. NAVIA, J. STOUT;
Andrews Univ., Berrien Springs, MI

Abstract: Female cricket Acheta domesticus exhibits selective phonotaxis in response to model calling songs with intensities above 75 dB and a carrier frequency of 4 - 5 kHz. When the animal is exposed to calling songs with varying syllable periods (30 to 90 ms), it is more likely to perform phonotaxis to calls with syllable periods that approach the most attractive range (50 - 70 ms), hence demonstrating its selectivity. On the contrary, it is less likely to respond phonotactically to calling songs with syllable periods that deviate from the most attractive range. Higher frequency sounds (16 kHz), have been reported to produce an aversive effect on the animal, reducing its likelihood of responding phonotactically to such calls. We hypothesized that an attractive calling song can become unattractive by adding a 16 kHz component to an already

existing 5 kHz call. In this experiment, young females (8 - 13 days old) were behaviorally tested to auditory stimuli consisting of single and dual frequencies: i) 5 kHz, 85 dB calling songs (30 - 90 ms), ii) 5 kHz, 85 dB + 16 kHz 45 dB and iii) 5 kHz 85 dB + 16 kHz 85 dB. The intensity of the 5 kHz component remained unchanged. Preliminary results suggest that in response to a dual frequency auditory stimuli, the animal is more likely to exhibit negative phonotaxis.

Disclosures: J. Mendonca: None. **B. Navia:** None. **J. Stout:** None.

Poster

637. Sensory and Motor Systems in Invertebrates

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Topic: F.04. Neuroethology

Support: Jeffress Foundation

Title: Crickets employ different escape strategies for different aversive stimuli

Authors: *C. L. CLELAND, A. M. CHILDS, K. L. REIMAN, R. L. GAITA, A. A. SIEBELS, A. M. SILVA, S. C. HEITSCH, C. R. EBEL, G. P. HOPKINS, J. C. SORIAGALVARRO; Biol., James Madison Univ., Harrisonburg, VA

Abstract: Animals respond to aversive stimuli with escape or withdrawal responses. In crickets, wind, which might normally be produced by an approaching predator, has been shown to evoke an escape response in which the cricket turns 180 degrees from the wind and then runs or jumps away. Similarly, looming stimuli that mimic the approach of a spider evoke similar turn and run responses. However, these results raise the question whether crickets utilize the same or a different strategy for noxious stimuli delivered directly to the cricket's leg. The goal of our research was to determine if crickets (Acheta domesticus) use the same or different strategies to escape from looming or heat stimuli delivered from different directions. Our results show that while crickets use a turning strategy for looming stimuli, they use a translational strategy for localized heat stimuli. Looming stimuli were created by attaching a 3" black polyurethane ball to the end of a 12" air cylinder (45 degrees to vertical) driven by compressed air. The direction of "attack" was varied in 45 degree increments around the cricket. In separate crickets, heat stimuli were delivered to each of the six tarsi with an infrared laser. The cricket's (n=60 crickets) response was recorded by a high-speed video camera (650 fps) from overhead. The top of the head, thoracic-abdominal junction and the tip of the abdomen were tracked over time to provide the two dimensional locations and orientation of the abdomen and the head/thorax. Further, the

initial locations of the tip of tarsi just prior to movement were recorded. Movement of the cricket was quantified in terms of turning and translation. In response to looming stimuli, crickets typically turned directly (180 degrees) away from the stimulus. Further, the response direction varied with the laterality of the stimulus. In contrast, crickets used a different strategy to escape from heat stimuli. Although they turned away from the side of the animal stimulated, the turn was small (~20 degrees) and did not depend on the laterality of the tarsi. In contrast, translation of the entire animal was directly away from the stimulus (180 degrees) and depended on the laterality of the tarsi stimulated. These results demonstrate that that the translational escape strategy used by crickets for heat stimuli is qualitatively different than the turning strategy used for looming strategy and suggests the hypothesis that the escape strategy used by insects may depend on whether the stimulus is local (e.g. tarsi) or global (e.g. wind).

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Poster

637. Sensory and Motor Systems in Invertebrates

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Topic: F.04. Neuroethology

Support: Lyman Briggs College Undergraduate Research Support

MSU Neuroscience Program Fellowship

Title: The roboscorpion-a method for inducing defensive behavior in giant desert hairy scorpions (hadrurus arizonensis)

Authors: *D. W. MILLER, G. GAGE;
Neurosci., Michigan State Univ., East Lansing, MI

Abstract: There is a significant lack of knowledge concerning the behavior of scorpions, despite being the largest biomass in several ecologies. Scorpions primarily access the world around them via mechanosensation, with legs highly sensitive to touch. Upon being touched, the scorpions engage in antipredator defensive behavior, which in this species entails movement away from the site of contact. By delivering positive voltage through silver wires implanted in the tarsal segment of H. arizonensis legs and exciting the leg?s mechanosensory neurons, the false

sensation of being touched can be induced in the scorpions. Utilizing the Backyard Brains Roboroach printed circuit board to provide electrical stimulation, up to 3.3 V and 65 Hz, to each of their legs in turn, multidirectional antipredator movement was induced and demonstrated in H. arizonensis.

Disclosures: D.W. Miller: A. Employment/Salary (full or part-time):; Backyard Brains. **G. Gage:** A. Employment/Salary (full or part-time):; Backyard Brains.

Poster

637. Sensory and Motor Systems in Invertebrates

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Topic: F.04. Neuroethology

Support: AFOSR Grant FA9550-10-1-0054

NSF Grant IOS-1120305

Title: Neural correlates of spatial attention in the central complex of the praying mantis (Tenodera sinensis)

Authors: *J. P. MARTIN[1], A. WOSNITZA[2], D. BERTSCH[2], J. W. BOSSE[2], A. J. POLLACK[2], R. E. RITZMANN[2];
[1]Dept. of Biol., [2]Biol., Case Western Reserve Univ., Cleveland, OH

Abstract: Attention to a region of space is central to the survival of a predator. Praying mantises track and stalk small, often cryptic prey using mainly motion cues. Here we report that this behavior shares features of spatial attention found in other animals including vertebrates. Mantises (Tenodera sinensis) were observed tracking live prey (cockroach nymphs) and prey simulated on an LCD monitor positioned under the clear floor of an arena. Mantises initially oriented to moving stimuli anywhere in their visual field. Once a particular target was foveated, 1) the mantis became insensitive to movement in the periphery of the visual field, 2) response delay to prey movement was shorter, and 3) responses to movement in the periphery gradually returned if the target stopped moving. Extracellular recordings from the CX of freely-moving mantises identified CX neurons broadly or narrowly tuned to movement in regions of the visual field. Once the mantis oriented to a target, a subset of CX neurons stopped responding to the movement of other prey in the periphery. Some neurons initially responsive to movement in the center and the periphery became responsive only to movement of the foveated prey. When the

target prey stopped moving, responses of these cells gradually returned, often before a behavioral response was observed. These results suggest a role for the insect central complex in a behaviorally- and ecologically- relevant context requiring spatial attention.

Disclosures: J.P. Martin: None. **A. Wosnitza:** None. **D. Bertsch:** None. **J.W. Bosse:** None. **A.J. Pollack:** None. **R.E. Ritzmann:** None.

Poster

637. Sensory and Motor Systems in Invertebrates

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 637.10/DD37

Topic: D.16. Posture and Gait

Support: NSTRF Training Grant NNX12AN24H

AFOSR Grant FA9550-10-1-0054

Title: Robotic model used to investigate descending commands during hunting of the mantis tenodera sinensis

Authors: *N. S. SZCZECINSKI, D. J. BERTSCH, J. P. MARTIN, R. D. QUINN, R. E. RITZMANN;
Mechanical Engin., Case Western Reserve Univ., Cleveland, OH

Abstract: Praying mantises perform visually-guided pivots to track and capture prey, actuating the head, thorax and legs to place the prey in the center of the visual field. Successful prey capture depends on the coordination of all leg joints with all of the body's degrees of freedom. In this behavior, neural mechanisms of sensorimotor integration interact with the biomechanics of the limbs to produce precise, rapid movement while maintaining equilibrium. To investigate these mechanisms, we have developed MantisBot, a robotic platform controlled by a real-time dynamic neural network model of insect thoracic ganglia circuits. The robot uses joint angle measurements from the servomotors and strain readings from each femur to produce posture. Rather than storing a map between body motion and leg joint angles, it commands its joints by fusing joint positions and load data with descending commands to pivot left or right. We use detailed, three-dimensional kinematics of the leg and body joints from high-speed video recordings of the animal to tune the neural network controller, ultimately achieving stable pivots that mimic the animal's movement. This hypothetical control structure can generate hypotheses

and test our understanding of how descending commands interact with motor circuits to produce visually-guided movements.

Disclosures: **N.S. Szczecinski:** None. **D.J. Bertsch:** None. **J.P. Martin:** None. **R.D. Quinn:** None. **R.E. Ritzmann:** None.

Poster

637. Sensory and Motor Systems in Invertebrates

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 637.11/DD38

Topic: F.04. Neuroethology

Support: NSF Grant IOS-1120305

AFOSR Grant FA9550-10-1-0054

Title: Change in hunting strategy is mediated by insulin in the praying mantis (Tenodera sinensis)

Authors: ***D. J. BERTSCH**[1], J. P. MARTIN[2], A. C. CARDWELL[2], R. E. RITZMANN[2]; [2]Biol., [1]Case Western Reserve Univ., Cleveland, OH

Abstract: Successful predation requires adapting hunting strategy to both internal and external contexts. Some species of praying mantis are primarily sit-and-wait or ambush hunters, but will actively pursue prey if they have been deprived of food. Here, we report the sensory and motor changes that accompany this switch between strategies. Starved mantises were observed in an open arena as they hunted live (cockroach nymphs) or simulated prey (on an LCD screen positioned below the clear floor of the arena). Starved mantises oriented to more distant prey than satiated animals, performed whole-body pivots of larger amplitude during tracking, and were more likely to pursue prey than sated animals. Injection of bovine insulin into the hemolymph of a starved animal produced similar increase in the threshold for responses to visual prey-like stimuli and reduced movement in comparison to saline-injected controls. Importantly, both sated and insulin-injected controls would still strike at and consume prey. We also report on insulin-induced changes in central complex (CX) responses to prey-like stimuli, and anatomical details of the insulin and short neuropeptide F pathway in the mantis brain. These results suggest that large switches in strategy can result from relatively simple changes in sensorimotor processing.

Disclosures: **D.J. Bertsch:** None. **J.P. Martin:** None. **A.C. Cardwell:** None. **R.E. Ritzmann:** None.

Poster

637. Sensory and Motor Systems in Invertebrates

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 637.12/DD39

Topic: F.04. Neuroethology

Title: Feeding network excitation drives a progressive reconfiguration of the turn motor network in a predatory sea-slug

Authors: *J. W. BROWN[1], R. GILLETTE[2];
[1]Col. of Med., [2]Mol. and Integrative Physiol., Univ. of Illinois at Urbana-Champaign, Urbana, IL

Abstract: Critical decisions in foraging for the predatory sea-slug *Pleurobranchaea californica* include approach-avoidance turning in response to salient stimuli and the suppression of turning during active, consummatory feeding. Our aim has been to elucidate the mechanisms of these actions by 1) identifying those elements in the feeding network that effect the reconfiguration of the turn network and 2) evaluating the roles played by a set of interneurons previously implicated in avoidance turning. It was previously shown that corollary output from the feeding network switched the polarity of the turn motor network from avoidance to orienting, thereby forming the basis of foraging approach-avoidance decisions. We found that members of a group of previously characterized buccal corollary discharge neurons activated during feeding exerted variable effects on turning behavior. In addition, bilateral avoidance turn command neurons, the A4s, were found to play no essential role in orienting turns. By contrast, bilateral serotonergic neurons known to modulate and sustain avoidance turns, the As2/3s, exhibited greater stimulus-driven activation when avoidance was converted to orienting turning. At sufficiently high levels of excitation in the feeding network, all identified turn elements were inhibited and turning was suppressed, consistent with suppression of turning during active feeding behavior. These results were synthesized in a model relating how interactions between the two networks drive foraging decisions.

Disclosures: **J.W. Brown:** None. **R. Gillette:** None.

Poster

637. Sensory and Motor Systems in Invertebrates

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 637.13/DD40

Topic: F.04. Neuroethology

Support: Research Experience for Undergraduates supplement in the summers of 2013 and 2014 to IIS-1965489

Title: Correlating kinetics and kinematics of earthworm peristaltic locomotion

Authors: *E. N. KANU[1], K. A. DALTORIO[2], R. D. QUINN[2], H. J. CHIEL[3];
[2]Mechanical & Aerospace Engin., [3]Biol., [1]Case Western Reserve Univ., Cleveland, OH

Abstract: The soft-bodied common earthworm, Lumbricus terrestris can bend and contort its body in response to its environment in order to navigate heterogeneous terrain and squeeze into narrow, constrained spaces. At the same time, the earthworm can exert forces radially and laterally against its environment to break up compacted soil, create and enlarge burrows, and resist extraction from its burrow by predators. In this poster, we quantitatively studied the coupling of kinematics and kinetics in earthworm peristalsis. We hypothesized there is a strong correlation between worm segment shape and variable, non-uniform load distribution of worm weight. Peristalsis, a wave of contractions that move posteriorly down the worm body, is the primary mechanism of earthworm locomotion. As segments contract laterally, they simultaneously increase circumferentially in diameter, while the segments anterior to them protrude laterally and decrease radially. We expect that, in order to minimize frictional drag losses, the segments with the widest diameter, being the “anchoring” segments (Miller 1988), will carry most of the load and consequently exert the maximum observed force normal to the ground. This leaves the non-contracting moving segments bearing the least amount of weight and thereby experiencing minimal frictional forces. This presumably leads to variable friction forces across the body. By utilizing video-tracking and measuring the vertical forces exerted by the worm segments while in motion, we correlated changes in segment shape to forces exerted by each segment. In our preliminary data, the anterior segments exhibit a correlation between segment diameter expansion and peak vertical forces exerted on the ground. The rear segments also exhibit variation in ground reaction forces; however, they display a more complicated relationship between segment expansion and exerted vertical force. Future work will explore this phenomenon. Understanding the way the worm exerts these forces may help us implement peristalsis in robots in diverse real-world environments.

Disclosures: E.N. Kanu: None. **K.A. Daltorio:** None. **R.D. Quinn:** None. **H.J. Chiel:** None.

Poster

637. Sensory and Motor Systems in Invertebrates

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 637.14/DD41

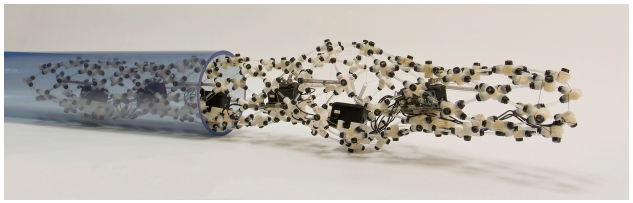
Topic: F.04. Neuroethology

Support: NSF, Grant No. IIS-1065489

Title: Design and actuation of compliant modular worm-like robot

Authors: *A. KANDHARI[1], A. D. HORCHLER[1], K. A. DALTORIO[1], K. C. MOSES[1], R. J. BACHMAN[1], H. J. CHIEL[2,3,4], R. D. QUINN[1];
[1]Mechanical and Aerospace Engin., [2]Dept. of Biol., [3]Biomed. Engin., [4]Neurosciences, Case Western Reserve Univ., Cleveland, OH

Abstract: Mimicking and better understanding the way an earthworm uses its many segments will help in designing new soft robots for a wide variety of applications. This is a challenging problem in robotics and biological insights can be valuable in both control and mechanical design. Here, we develop a new type of robotic platform for investigating these problems: Compliant Modular Mesh Worm (CMMWorm). The robot's body utilizes a compliant mesh that couples decreases in diameter with increases in length. The function of the mesh parallels the hydrostatic skeleton of an earthworm. Because of this diameter-length coupling, as waves of radial contraction travel down the cylindrical body, our robot advances along ground or in pipes with peristaltic locomotion. The mesh consists of rhombuses whose sides are polycarbonate rods or nylon tubes. The vertices of the mesh are 3-D printed and permit pin-joint rotation of the rhombus sides. Each segment of the robot is individually controlled using a smart servo actuator attached to cables for both longitudinal (contraction) and circumferential (extension) motion. The modular mesh enables the robot to achieve a large strain range comparable to that of an earthworm. In an earthworm, the minimum segment diameter is 50-60% smaller than its maximum diameter, while the mesh of CMMWorm is capable of actively deforming 52% relative to its maximum diameter. With six segments, our modular robot can crawl on smooth, flat substrates and pipes. The smart servos provide load sensing, which in combination with simple kinematic models, can provide the basis for responsive behaviors. Individual segments can detect the wall of a pipe, estimate its diameter, and return to its initial position using a load-sensing algorithm. To provide immediate response to multisensory perturbations while coordinating multiple degrees of freedom, we are exploring stable heteroclinic cycles (SHCs) as a dynamical architecture. CMMWorm is an ideal platform for comparing the performance of SHCs with finite state machines and limit cycle oscillators.



Disclosures: **A. Kandhari:** None. **A.D. Horchler:** None. **K.A. Daltorio:** None. **K.C. Moses:** None. **R.J. Bachman:** None. **H.J. Chiel:** None. **R.D. Quinn:** None.

Poster

637. Sensory and Motor Systems in Invertebrates

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 637.15/DD42

Topic: F.04. Neuroethology

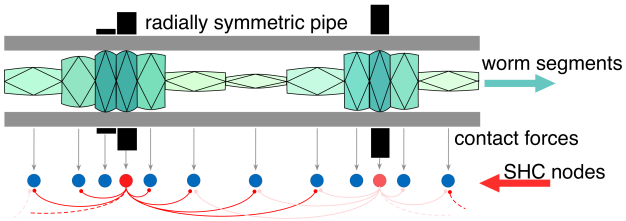
Support: NSF Grant IIS-1065489

Title: Controller design for a soft-bodied peristaltic locomotion robot

Authors: ***K. A. DALTORIO**[1], A. D. HORCHLER[1], A. KANDHARI[2], H. J. CHIEL[3], R. D. QUINN[1];
[1]Mechanical Engin., [3]Biol., [2]Case Western Reserve Univ., Cleveland, OH

Abstract: The type of soft-body locomotion used by earthworms and slugs could be valuable for robots that inspect pipes, crawl through collapsed tunnels, or assist in endoscopy. The sequential pattern of muscle contraction that generates this motion is called peristalsis. However, if the pattern of rearward traveling waves is not responsive to the environment, the body's progress will be stalled by small obstacles, changes in diameter of the substrate, or other irregularities. Here, we have designed a responsive controller based on a mutually inhibitory dynamic architecture in a simplified simulation environment that determines body segment actions based on contact feedback. Control and simulation of worm robots is notoriously challenging because of their many ground contacts, hyper-redundancy, and highly nonlinear and interdependent deformation. Our simulation uses several simplifying assumptions to make this problem tractable including: 1) each segment is a simple rhombus whose increases in length cause decreases in height, 2) stiffness interdependence is limited to nearest neighboring segments, 3) contact forces are modeled with Coulomb dry friction and can be sensed by the controller, and 4) the robot and surrounding environment are radially symmetric. The controller determines how to apply actuation forces to each segment rhombus. Stable heteroclinic channels (SHCs) are continuous

dynamical systems capable of generating rhythmic output of varying period in response to sensory inputs or noise. This feature can be used to control state transitions smoothly. Here, each segment must anchor, extend, or retract. The contact feedback is connected to the SHC, which controls the timing of transitions between these actions. We demonstrate that our SHC controller allows for improved adaptation to a change in pipe diameter with more rapid movement and less energy loss. In an example narrowing pipe, this controller loses 40% less energy to slip compared to the best-fit sine wave controller. This controller design informs our ongoing biological experiments and robotic worm designs.



Disclosures: **K.A. Daltorio:** None. **A.D. Horchler:** None. **A. Kandhari:** None. **H.J. Chiel:** None. **R.D. Quinn:** None.

Poster

637. Sensory and Motor Systems in Invertebrates

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 637.16/DD43

Topic: F.04. Neuroethology

Support: EMBO Long Term Fellowship ALTF 345-2014

Simons Collaboration on the Global Brain

Title: Brain-wide attractor dynamics represent the motor command sequence in *C. elegans*

Authors: ***S. KATO**, H. KAPLAN, T. SCHRODEL, M. ZIMMER;
IMP - Res. Inst. of Mol. Pathology, Vienna, Austria

Abstract: Behavior is a continuous output of the nervous system, yet a prevailing approach to describe behavior defines discrete modules assembled into action sequences. This raises the question of how this higher level of organization might be represented by neural activity. Using single-cell resolution brain-wide calcium imaging in Caenorhabditis elegans, we show that the continuous, spontaneous activity of most interneurons and motor neurons in the worm brain

organizes into widely shared, coordinated population dynamics. The neural state evolves as a cyclical trajectory, tracing out a sub-volume, or manifold, indicative of attractor-like dynamics. Distinct regions of the manifold capture differential neuronal recruitment patterns; the participating neurons exhibit cell class-specific phase relationships with the global oscillation. We imaged the activity of representative neurons in freely moving animals and found that they reliably encode both motor behavioral state and graded metrics of motion, like crawling speed and posture. This information enables us to map instantaneous brain state, on a single-trial basis, to motor command state. Decisions between alternate behavioral commands manifest as branching trajectory bundles. The neural state manifold is robust to decoupling from motor output, as well as salient sensory input, which entrained the global brain oscillation. Both results indicate that the time evolution of behavioural commands is stably maintained by intrinsic population dynamics. Directional flow on the manifold corresponds to the temporal sequence of actions, thereby establishing a continuous embedding of the action sequence in neural state space. This study defines the function of the global brain signal in this system: to maintain a representation of the holistic motor command sequence.

Disclosures: **S. Kato:** None. **H. Kaplan:** None. **T. Schrodel:** None. **M. Zimmer:** None.

Poster

637. Sensory and Motor Systems in Invertebrates

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 637.17/DD44

Topic: F.04. Neuroethology

Support: European Commission EP-7 project OCTOPUS (grant agreement #231608)

European Commission EP-7 project STIFF-FLOP (grant agreement #287728)

Title: Octopuses hold their head in a fixed horizontal orientation relative to the world likely to simplify the control of locomotion with flexible arms

Authors: ***G. LEVY**, B. HOCHNER;
Dept. of Neurobio., The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Octopus vulgaris has a soft body lacking any rigid skeleton and a very complicated morphology, including eight long, slender, flexible arms. Each arm has an enormous number of degrees of freedom (DOFs) and is thus very complicated to control. Due to the very flexible body, the position and posture of the head relative to the motoric system (the arms) is highly

variable and thus could be a hindrance for locomotion control that must coordinate the motoric and visual systems. Here we analyzed the kinematic parameters of the posture of the octopus head during various spontaneous and evoked behaviors. Octopuses were videotaped with two or three video cameras positioned at different angles. Video images were loaded into dedicated Matlab software we developed specifically to analyze octopus head position, posture, and orientation. Reconstructing the 3D position of the eyes in each time frame revealed that during all behavior octopuses always keep the head horizontally orientated relative to the ground, regardless of substrate slope or orientation; the two eyes, which lie at a fixed position in the head, were always at the same height relative to the ground. This means that octopuses keep their visual system at a fixed 2D horizontal orientation relative to the world. This head orientation is maintained even when some arms are in contact with fixed reference points during crawling, standing, and walking. Because the octopus head cannot appreciably move or rotate relative to the body and the arm bases, the orientation of the head is controlled only by the arms (while they are supporting the body). Therefore, the orientation of the head must be continuously controlled by dynamically adjusting the chord distance between the point of contact of the arm with the supporting environment and the head. Fine adjustment of the chord length can be achieved, for example, by controlling the level of arm stiffness. It is most likely that head orientation relative to gravity is controlled by the statocysts of the octopus vestibular system. Our results therefore imply that the statocysts are an important part of the motor programs controlling the arms during the various locomotory and static behaviors. Using the statocysts simplifies arm control as it constrains the number of DOFs in the interaction of the arms with the environment. In addition, the fact that the sensory and motor control centers in the head are at a fixed reference position relative to the world reduces the number of DOFs involved in the interactions of the octopus with the environment.

Disclosures: **G. Levy:** None. **B. Hochner:** None.

Poster

637. Sensory and Motor Systems in Invertebrates

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 637.18/DD45

Topic: F.04. Neuroethology

Support: Groner Foundation

Title: A surprisingly rich behavioral repertoire for an animal without a brain - the sea anemone Stomphia coccinea

Authors: *W. N. FROST[1], R. T. PORTER[2], Y. ISMAIL[2];
[1]Dept Cell Biol. and Anat., The Chicago Med. Sch., North Chicago, IL; [2]Dept. Biol., Lake Forest Col., Lake Forest, IL

Abstract: Sea anemones are considered to be the first group of organisms in animal evolution exhibiting a nervous system. They have no brain or CNS. Instead, they make do with a primitive nerve net consisting of diffusely distributed neurons. Like all anemones, *Stomphia coccinea* uses stinging nematocysts on its tentacles to subdue and capture prey. *Stomphia* is also well known for its remarkable ability, unusual in anemones, to flee from its own predators by detaching and then swimming via a series of alternating body flexions that propel it away to safety. Intrigued by its ability to generate such complex behavior with a nonspecialized, diffuse nerve net, we decided to more fully characterize *Stomphia's* behavioral repertoire. This involved comparing its responses to two very different predators: the seastar *Dermasterias imbricata* and the nudibranch mollusk *Aeolidia papillosa*, an anemone specialist. Several responses of eight Stomphia to each of these predators were filmed. Stomphia's response to *Dermasterias* was always defensive, consistent with prior literature, and consisted of rapid tentacle withdrawal and oral disk closure, followed by column extension, pedal disk detachment, and swimming. Prior reports have also documented escape swimming of *Stomphia* to *Aeolidia*. Comparing the responses to the two predators, we found that *Stomphia* employed a very different strategy upon detecting *Aeolidia*. In the large majority of encounters, *Stomphia* responded aggressively, with one or more directed bends to sting the predator. This was often followed by rapid withdrawal of the tentacles and closure of the oral disk for 10s of seconds, after which the anemone frequently reemerged to attack again. Occasionally it would also bend over and whirl its tentacles around the column base, sweeping them in a circular search pattern. Most of the time these attack behaviors were successful at driving away the nudibranch. In a third of the cases (10 of 33) they weren't, and *Stomphia* switched tactics by detaching and swimming away. Collectively, these observations indicate that *Stomphia* employs two very different behavioral strategies in response to the two predators. To the larger sea star it always flees. To the smaller nudibranch *Stomphia* nearly always attacks first, often driving it off. If unsuccessful, it then switches strategies and flees. These diverse behavioral strategies are impressive for an animal equipped with only a diffuse nerve net.

Disclosures: W.N. Frost: None. **R.T. Porter:** None. **Y. Ismail:** None.

Poster

637. Sensory and Motor Systems in Invertebrates

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 637.19/DD46

Topic: F.04. Neuroethology

Support: This material is based upon work supported by the National Science Foundation under Cooperative Agreement No. EPS-1003907.

Title: Impacts of elevated environmental manganese on crayfish behavior and neurophysiology

Authors: A. C. LEFEVRE, A. PARSONS-WHITE, *B. L. ANTONSEN;
Biol. Sci., Marshall Univ., Huntington, WV

Abstract: Each year millions of tons of manganese (Mn) are extracted for use in steel production, which is a vital part of the Appalachian region's economy. However, the Mn that is deposited into the air and water ways during manufacturing could be harmful to the health of residents in the area. Although Mn is an essential nutrient, high amounts of Mn in the water and air have shown to have neurotoxic effects in humans with symptoms similar to those of Parkinson's disease and ADHD, such as, tremors, disrupted balance, and hyperactivity. The EPA has a maximum allowable concentration of 0.05 ppm for drinking water, but currently there are no federally recommended aquatic life criteria for Mn. Concentrations exceeding 10 ppm have been detected in surface streams near mining activities. This research involves determination of the effects elevated Mn has on the escape response and relevant neurotransmitter distribution/concentration of crayfish. Because crayfish are a keystone species, negative effects on their behavior can cause disruption to entire ecosystem. Crayfish are exposed to ecologically relevant concentrations of Mn, up to 10 ppm for chronic (2 week) and acute (2 day) periods to simulate chronic exposure downstream from industrial sites and from runoff or spills that are short term, respectively. Crayfish are exposed in aquaria and are tested for latency to, duration of, and trajectory of first tail flip. Nerve cords are then removed and immunolabeled for serotonin and dopamine, because these neuromodulators are known to influence changes in crayfish posture and motor control. Crayfish treated with low levels of Mn for acute exposure times did not show any detectable behavioral change. However, chronic exposure effects escape trajectory and latency. A dose dependent response is seen in chronically treated crayfish where latency decreases as concentration of Mn increases. This suggests that elevated concentrations of Mn may lead to increased escape circuit excitability in crayfish.

Disclosures: A.C. Lefevre: None. **A. Parsons-White:** None. **B.L. Antonsen:** None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 638.01/DD47

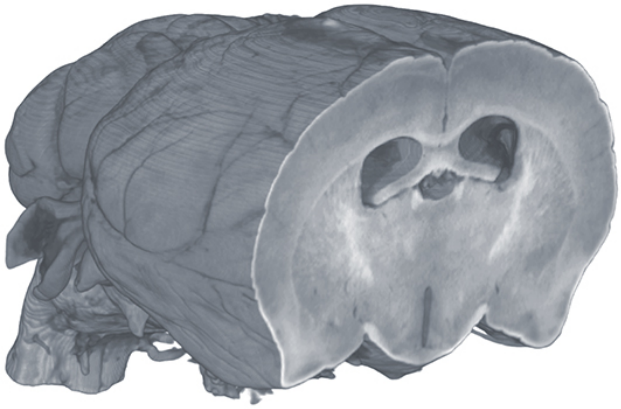
Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: Max Planck Society

Title: Advances in high-resolution, high-throughput whole mouse brain volume electron microscopy

Authors: ***S. MIKULA**[1], S. K. MIKULA[1], M. MUELLER[1], N. NEEF[2], J. TISLER[1], J. TRITTHARDT[1], W. DENK[1];
[1]Electrons - Photons - Neurons, Max-Planck Inst. For Neurobio., Martinsried, Germany; [2]Max-Planck Inst. For Med. Res., Heidelberg, Germany

Abstract: Currently only electron microscopy provides the resolution necessary to reconstruct neuronal circuits completely and with single-synapse resolution. Because almost all behaviors rely on neural computations widely distributed throughout the brain, a reconstruction of brain-wide circuits and ultimately the entire brain is highly desirable. However, these reconstructions require the undivided brain to be prepared for electron microscopic observation. Recently, a preparation, BROPA (brain-wide reduced-osmium staining with pyrogallol-mediated amplification), was described that results in the preservation and staining of ultrastructural details throughout the brain at a resolution necessary for tracing neuronal processes and identifying synaptic contacts between them (Mikula & Denk, 2015). Here, we present recent progress towards volume imaging the whole mouse brain using a high-throughput (>1 GHz imaging rate) 91-beam scanning electron microscope, a custom-built in-vacuo whole-brain microtome and an evaporative metal coater, all of which are integrated into a fully automated workflow using an in-chamber robot. Our method may be suitable for generating a high-resolution whole mouse brain volume electron microscopy dataset that would serve as the basis for a complete neural circuit reconstruction. This work was funded by the Max Planck Society.



Disclosures: **S. Mikula:** None. **S.K. Mikula:** None. **M. Mueller:** None. **N. Neef:** None. **J. Tisler:** None. **J. Tritthardt:** None. **W. Denk:** None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 638.02/DD48

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: ERC Grant MULTICONNECT 639938

Title: Human brain anatomy post mortem with a whole-brain 9.4T RF-coil: towards mesoscale resolution with MRI

Authors: *A. ROEBROECK[1], S. SENGUPTA[1], M. BASTIANI[1], S. SCHILLAK[4], B. TRAMM[4], M. WAKS[4], A. LATASTER[2], A. HERRLER[2], D. TSE[3,5], B. POSER[1]; [1]Cognitive Neurosci., [2]Dept. of Anat. & Embryology, [3]Dept. of Neuropsychology and Psychopharmacology, Maastricht Univ., Maastricht, Netherlands; [4]Life Services, LLC, Minneapolis, MN; [5]Dept. of Radiology, Maastricht Univ. Med. Ctr., Maastricht, Netherlands

Abstract: Introduction The investigation of whole human brains post mortem with large bore MRI systems can achieve resolution considerably superior to that achievable in-vivo. Here the aim is i) to design and construct a specialized 9.4T 8Ch parallel transmit (pTX), 24Ch receive RF-coil for whole post mortem human brains and ii) to show that its use in pTX-mode enables high resolution anatomical imaging of the whole human brain. **Methods** A single formalin fixed human brain was used from a male donor giving informed consent under the Maastricht University, Department of Anatomy & Embryology Body donation program (death to formalin fixation: ~12h, fixation to scanning: ~12 months). A 3D conformal container for post mortem human brains was created and a former (accommodating 24Ch RX and 8Ch TX) was modeled around the container (fig. 1A). Experiments were performed with a 9.4T 820cm bore human MR scanner (Magnetom 9.4T, Siemens Medical Solutions, Erlangen, Germany). High resolution MRI was performed with a 3D gradient echo pulse sequence with a kt-points pTX pulse [1] with imaging parameters: matrix 448x510x448, FA=6deg, 4avgs. T1w: TR=8.4ms, TE=3.6ms TA=1h49m; T2*w: TR=32ms, TE=10,15,20,25ms, TA/echo=7h09m. **Results & Conclusion** High signal and contrast is achieved at high resolution in the entire brain with T1 weighted (fig. 1B) and T2* weighted (fig. 1C) contrast. PTX Homogenized RF fields enable stable contrast with enough detail to distinguish hippocampal layering and cerebellar folia. The constructed imaging setup for whole post mortem human brains, which combines a high magnetic field (9.4T), specialized RF-coil and parallel transmit, enables high resolution neuroanatomical investigations of the intact human brain. **References** 1.Cloos, M.A., et al. Magn Reson Med, 2012. 67(1): p. 72-80.

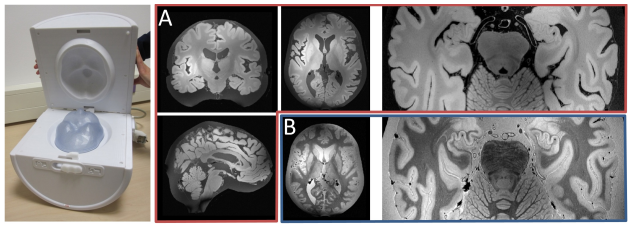


Figure 1 A) The container in the opened RF-coil array, showing matching geometry. A&B) Whole brain 3D GE acquisitions at 330μm isotropic A) coronal, transverse and saggital planes (left) and zoom-in of the T1w data. B) transverse plane (left) and zoom-in of the T2*w data.

Disclosures: **A. Roebroeck:** None. **S. Sengupta:** None. **M. Bastiani:** None. **S. Schillak:** None. **B. Tramm:** None. **M. Waks:** None. **A. Lataster:** None. **A. Herrler:** None. **D. Tse:** None. **B. Poser:** None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 638.03/DD49

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: China MOST grants 2012CB837703

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China MOST grants 2012YQ03026005

NNSFC 91432114

Title: Whole brain mapping of the direct inputs and axonal projections of pomc and agrp neurons

Authors: *D. WANG;
Natl. Inst. of Biol. Sci., Beijing, China

Abstract: Pro-opiomelanocortin (POMC) neurons in the arcuate nucleus (ARC) of the hypothalamus and nucleus tractus solitarius (NTS) of the brainstem play important roles in suppressing food intake and maintaining energy homeostasis. Previous tract-tracing studies have revealed the axonal connection patterns of these two brain areas, but the intermingling of POMC neurons with other neuron types has made it challenging to precisely identify the inputs and outputs of POMC neurons. In this study, we used the modified rabies virus to map the brain areas that provide direct inputs to the POMC neurons in the ARC and NTS as well as the inputs to the ARC AgRP neurons for comparison. ARC POMC neurons receive inputs from dozens of

discrete structures throughout the brain, and mainly from the hypothalamus. The brain areas containing the presynaptic partners of ARC POMC neurons largely overlap with those of ARC AgRP neurons, although POMC neurons receive relatively broader, denser inputs, which suggest ARC POMC and AgRP neurons may be regulated by some similar upstream nuclei. Furthermore, the direct inputs to POMC neurons in the NTS are predominantly located in the brainstem, demonstrating very different innervation patterns for POMC neurons in the ARC and NTS, which may explain their functional differentional, especially in regulating energy metabolism. By selectively expressing fluorescent markers in the ARC and NTS POMC neurons, we also found that almost all of their major presynaptic partners are innervated by POMC neurons in the two areas, suggesting that there are strong reciprocal projections among the major POMC neural pathways. Overall, our data depicted the whole-brain connections of the projection neurons of the central melanocortin system in a cell-type-specific manner. More importantly, POMC and AgRP neurons are involved in multiple physiological functions and behaviors, thus a comprehensive mapping of their connections lays the foundation for studying the functional roles of specific neural pathways.

Disclosures: D. Wang: None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 638.04/DD50

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NIH/NINDS/NIMH 1R01NS092474

NIH/NIBIB 1R01EB016411 (CRCNS)

NIH 1R01DA036400 (BIGDATA)

Title: The open synaptome project: toward a microscopy-based platform for single-synapse analysis of diverse populations of cns synapses

Authors: *S. J. SMITH[1], R. BURNS[2], M. CHEVILLET[3], E. LEIN[1], G. SAPIRO[5], W. SEELEY[6], J. TRIMMER[7], J. T. VOGELSTEIN[4], R. WEINBERG[8];
[1]Allen Inst. For Brain Sci., Seattle, WA; [2]Computer Sci., [3]Applied Physics Lab., [4]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [5]Electrical and Computer Engin., Duke Univ.,

Durham, NC; [6]Univ. of California, San Francisco, CA; [7]Univ. of California, Davis, CA; [8]Cell Biol. and Physiol., Univ. of North Carolina, Chapel Hill, NC

Abstract: New light and electron microscopy methods are now enabling the first structural and molecular measurements across large CNS synapse populations at the single-synapse level. Accumulating evidence that CNS synapses are highly diverse in structure, protein composition, function, and neuropathologic susceptibility points to an urgent need for integrated "synaptomic" survey tools. The Open Synaptome Project (OSP; http://opensynapto.me) is an endeavor of a consortium of investigators at the Allen Institute, Johns Hopkins, Johns Hopkins Applied Physics Laboratory, UNC Chapel Hill, Duke, UC Davis and UC San Francisco aimed at building broadly accessible foundations for single-synapse analysis of CNS synapse populations. Our current efforts concentrate on advancing and disseminating methods for array tomography (ATomo) immunofluorescence microscopy, as these seem especially suitable for high-throughput proteometric analysis of the diverse and volumetrically dense synapse population encountered in the mammalian CNS. Given the importance of mouse models of human brain function and human mental and neurological disorders, the OSP's initial work focuses on neocortical structures in mouse and human. The goal is to build an open and broadly useful platform to more quantitatively understand similarities and differences between CNS synapse populations in those species. The OSP's present work includes efforts to (1) improve methods for preparing specimens of mouse and human neocortex for ATomo analysis, (2) expand and validate synapse-relevant antibody panels, (3) develop faster and more automated ATomo imaging methods, (4) deploy advanced petascale image database methods, (5) improve methods for automated synaptomic analysis of ATomo image data, (6) develop cell-biologically principled taxonomies of mouse and human synapse types, and (7) establish web portals for sharing of methods, data, taxonomies, and other resources across broad communities of synapse biologists and for any other neuroscientists grappling with basic mechanisms and disorders of synaptic network function. This poster describes OSP status in each of these areas. See neighboring posters for more details.

Disclosures: **S.J. Smith:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Founder's equity in Aratome, LLC, a Menlo Park CA company that provides array tomography products and services. **R. Burns:** None. **M. Chevillet:** None. **E. Lein:** None. **G. Sapiro:** None. **W. Seeley:** None. **J. Trimmer:** None. **J.T. Vogelstein:** None. **R. Weinberg:** None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 638.05/DD51

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NIH NINS/NIMH 1R01NS092474 (TRA)

NIH 1R01DA036400 (BIGDATA)

NIH/NIBIB 1R01EB016411 (CRCNS)

DARPA N66001-14-1-4028 (GRAPHS)

NIMH

DARPA Neuro-FAST

Title: Computational statistics for whole brain CLARITY analysis using the Open Connectome Project

Authors: *A. K. SIMHAL[1], W. GRAY RONCAL[4], K. A. LILLANEY[5], K. KUTTEN[6], M. I. MILLER[6], J. T. VOGELSTEIN[6], R. BURNS[5], L. YE[7], R. TOMER[7], K. DEISSEROTH[7], G. SAPIRO[2,3];
[2]Electrical and Computer Engin., [3]Biomed. Engin., [1]Duke Univ., Durham, NC; [4]Applied Physics Lab. of Johns Hopkins Univ., Laurel, MD; [5]Computer Sci., [6]Dept. of Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [7]Dept. of Bioengineering, Stanford Univ., Palo Alto, CA

Abstract: New experimental technologies are rapidly changing the nature of data available in neuroscience. These techniques are yielding big neuroscience data: For example, CLARITY allows imaging of the whole mouse brain at micrometer resolution, requiring ~500 gigabytes of storage. Even large workstations are unable to load the entire datasets into memory, therefore breaking the standard data analytic workflow. We present here an alternative strategy using the Open Connectome Project (OCP) infrastructure. First, we ingest each raw dataset into its own OCP database, building an image pyramid including isotropic resolutions, and store on our high-throughput data store. This enables Webvisualization capabilities, including pan and zoom in orthogonal cutting planes. The images were registered to the Allen Institute's Mouse Brain Atlas using nonlinear registration (Bsplines based nonlinear multiresolution registration strategy). Then, for each region of interest, we compute contrast and text features. The texture analysis features act directly on the raw data, avoiding the challenging preprocessing of detecting activation via unknown and data/region-dependent thresholds. Features were clustered, and the quality of clustering was evaluated using Adjusted Rand Index. We found that a small number of features (13) are sufficient for accurate classification among the classes of data (Figure 1). Moreover, the methods developed for this application are readily applied to other datasets. To that end, all data, code, and data derivatives will be made available after publication through the OCP website, http://openconnecto.me.

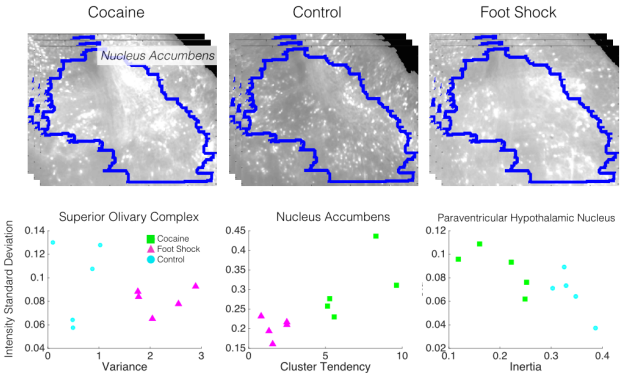


Figure 1: First row: Nucleus Accumbens under the 3 conditions. Second row: three pairwise comparison plots demonstrating accurate class separation.

Disclosures: A.K. Simhal: None. **W. Gray Roncal:** None. **K.A. Lillaney:** None. **K. Kutten:** None. **M.I. Miller:** None. **J.T. Vogelstein:** None. **R. Burns:** None. **L. Ye:** None. **R. Tomer:** None. **K. Deisseroth:** None. **G. Sapiro:** None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 638.06/DD52

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NIH/NIBIB 1R01EB016411 (CRCNS)

NIH 1R01DA036400 (BIGDATA)

DARPA N66001-14-1-4028 (GRAPHS)

NIH NINS/NIMH 1R01NS092474 (TRA)

DARPA XDATA program of DARPA administered through Air Force Research Laboratory contract FA8750-12-2-0303

Endeavor Scientist Training Fellowship Child Mind Institute

Title: Open connectome project: lowering the barrier to entry big data neuroscience

Authors: *J. T. VOGELSTEIN[1], S. J. SMITH[2], W. GRAY RONCAL[3], R. VOGELSTEIN[4], R. BURNS[1], K. A. LILLANEY[1], A. D. BADEN[1], G. KIAR[1], P. MANAVALAN[3];

[1]Johns Hopkins Univ., Baltimore, MD; [2]Allen Inst. for Brain Sci., Seattle, WA; [3]Johns Hopkins Applied Physics Lab., Laurel, MD; [4]IARPA, Laurel, MD

Abstract: Recent technical progress allows neuroexperimentalists to collect ever more detailed and informative anatomical and physiological data from brains of all sizes. With classical approaches it was feasible for neuroscientists to draw their results on paper, but modern experiments are amassing terabytes of data. These datasets span experimentally accessible spatiotemporal scales, ranging from nanometers to meters, and millisecond to monthly sampling rates. These large datasets create significant challenges for our community at every step of the data analysis pipeline, including (i) image data storage and management, (ii) metadata capture, (iii) visualization, (iv) image pre-processing, (v) scene parsing, (vi) statistical analysis, and (vii) dissemination. The *Open Connectome Project* has been developed to lower the barrier to entry into big data neuroscience. We have designed and built a computational ecosystem to enable petascale neuroscience. This includes several reference workflows, including images-to-graphs from various experimental paradigms, ranging from serial electron microscopy to multimodal MRI. Moreover, anyone in the world with Internet access can now visualize, download, analyze, upload, or otherwise interact with all public datasets. We are in the process of scaling up the number of datasets, the range of experimental modalities, and the Web-services we enable. We are now embarking on a new thread called the Open Synaptome Project (http://opensynapto.me) which will provide joint electron microscopy, immunofluorescence, and physiology data across species, at sub-micrometer resolution. Work underway will provide pre-packaged cluster environments—1-click deployable on local or commercial cloud computing infrastructures—so that others can replicate and modify our services internally. All of our code and data are available online at http://openconnecto.me, in accordance with open science standards. Please come to our poster or booth if your current scientific workflows are breaking under the weight of big data.

Disclosures: J.T. Vogelstein: None. **S.J. Smith:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aratome. **W. Gray Roncal:** None. **R. Vogelstein:** None. **R. Burns:** None. **K.A. Lillaney:** None. **A.D. Baden:** None. **G. Kiar:** None. **P. Manavalan:** None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 638.07/DD53

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: FWF P 23102-N22

Title: Light sheet microscopy of whole mouse brains with improved clearing and optics

Authors: *H.-U. DODT[1,2], C. HAHN[1,2], K. BECKER[1,2], S. SAGHAFI[1], N. JÄHRLING[1,2], M. PENDE[1,2], I. SABDYUSHEVA LITSCHAUER[2], M. WANIS[1];
[1]Tech. Univ. Vienna, Vienna, Austria; [2]Med. Univ. Vienna, Vienna, Austria

Abstract: Visualization of complete neuronal networks in the brain is an important goal of neuroscience. To this end clearing and recording of mouse brains with light sheet microscopy has become increasingly popular in recent years. Various water based clearings have been developed which have certain advantages like good fluorescence preservation but also certain disadvantages like incomplete clearing or complicated and unreliable procedures. We developed the first brain clearing 8 years ago which was then based on organic solvents. By clearing neuronal tissue with benzyl alcohol and benzyl benzoate (BABB) after dehydration, we could visualize GFP-labelled neuronal networks in the whole brain (Dodt et al., 2007). Improving our clearing technology by using tetrahydrofuran (THF) for dehydration and dibenzylether (DBE) for clearing (3DISCO) we were able to image GFP-labelled axons even in heavily myelinated neocortex and spinal cord (Becker et al., 2012, Ertürk et al. 2012). However both BABB and DBE based clearings quench GFP fluorescence to a certain extent, making it necessary to keep clearing times as short as possible and eventually compromising complete clearing. We found now a way to stabilize GFP fluorescence in DBE for weeks with neglegible bleaching during recording by sDISCO (stabilized 3DISCO clearing). With sDISCO we were able to visualize very delicate neuronal structures like the finest neuronal branches of the axonal network in the neocortex as well as dendritic spines. As the sDISCO clearing procedure is very reliable and the cleared brains are very solid and stable we expect sDISCO to become a standard procedure for brain clearing. In addition we developed optical devices for correcting existing air objectives used for imaging of brains in clearing solutions. To improve the axial resolution of our recordings we further developed optics for the generation of longer and thinner light sheets. The resistance to bleaching in the sDISCO clearing allowed us to record and combine several images for every optical section with laterally shifted best fields of view of the light sheet (x-focussing). With the combination of improved clearing and improved optics we were able to record neuronal networks in mouse brains with unprecedented details.

Disclosures: H. Dodt: None. **C. Hahn:** None. **K. Becker:** None. **S. Saghafi:** None. **N. Jährling:** None. **M. Pende:** None. **I. Sabdyusheva Litschauer:** None. **M. Wanis:** None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 638.08/DD54

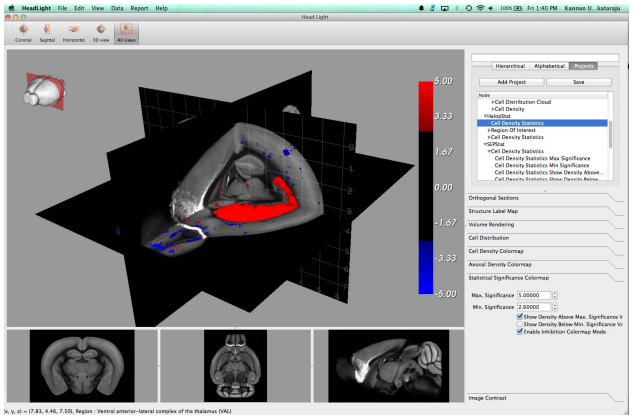
Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NIH Whole Mouse Brain 1U01MH105971

Title: HeadLight: A tool chain to analyze & visualize whole mouse brain data

Authors: *K. UMADEVI VENKATARAJU[1,2], A. NARASIMHAN[1], P. OSTEN[1], Y. KIM[1], J. TARANDA[1], L. KADIRI[2];
[1]Osten Lab., Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Certerra Inc., Cold Spring Harbor, NY

Abstract: With the advent of whole brain imaging techniques, there is necessity to develop methods to analyze and visualize these datasets. The tool chain "HeadLight" will provide necessary tools to create an whole brain atlas, do automated cell counting and visualize the counting. Firstly, the registration part will help to register a reference brain to other brains imaged using a new imaging assay and further to port the markups of existing atlas labels to the newly generated atlases. Such atlases give the ability to compare datasets spatially in the same reference space. Secondly, we propose 2D and 3D cell counting methods to count cells in these brains using deep learning algorithms. Finally to visualize the datasets, we propose an cross platform utility built based on CMake, C++, ITK and VTK. It has the ability to see cell distribution patterns in the whole brain, compute cell density measurements, axonal densities and finally visualize statistical significance analysis. The tool also has capabilities for visual query on these datasets. In the last few years, many methods have been invented to study the mouse brain with optical imaging methods. These assays are a combination of novel optical clearing methods and microscopy techniques. We propose to quantify the variabilities in these procedures by establishing ground truth and methods to measure these metrics. In this method, we propose to use an MRI atlas as ground truth to define variabilities in shape and size of the mouse brain. We define the shinkage/bloat in various regions of the brain by calculating the dice coefficient of the same region before and after registration. We further want to quantify the efficiency of optical clearing or immunostaining penetration by measuring cell counts of the proposed assays compared to ground truth from a similar brain imaged using serial two-photon tomography. The analysis and visualization are done using HeadLight tool chain.



Disclosures: **K. Umadevi Venkataraju:** A. Employment/Salary (full or part-time):; Part-time. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Certerra Inc.. **A. Narasimhan:** None. **P. Osten:** None. **Y. Kim:** None. **J. Taranda:** None. **L. Kadiri:** None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 638.09/DD55

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: Swedish Brain Foundation (Hjärnfonden)

Title: A whole-brain atlas of inputs to inhibitory and excitatory neurons in prefrontal cortex

Authors: ***Y. XUAN**, S. ÄHRLUND-RICHTER, D. FÜRTH, K. MELETIS, M. CARLÉN; Dept. of Neurosci., Karolinska Institutet, Stockholm, Sweden

Abstract: Prefrontal cortex (PFC) is involved in various aspects of cognition, including attention, memory and decision-making. Those processes are shaped both by the balance of inhibitory and excitatory actions in the local network and by long-range inputs from other brain regions. We map for the first time the whole-brain input circuitry controlling three central populations of inhibitory (parvalbumin, somatostatin and vasointestinal peptide expressing) and excitatory (calcium/calmodulin-dependent protein kinase IIα expressing) neurons in PFC. We have developed a two-vector system (one adeno-associated virus (AAV) and one rabies vector) for retrograde tracing of monosynaptic inputs to genetically defined populations of neurons. The

AAV has been modified to enable reliable identification of starter cells and the EGFP expressing input neurons can be plotted in the three dimensional space onto a reference atlas using our recently developed software suit[1]. Our preliminary data shows that the three types of inhibitory neurons and the excitatory neurons receive a surprisingly high degree of similar inputs. The main input to both excitatory and inhibitory neurons in PFC is derived locally, but all four types also receive extensive long-range input from the rest of cortex. Sub-cortically the basal forebrain and thalamus provide most prominent input. We found a distinct subpopulation of globus pallidus (GP) neurons, which sits along the border with internal capsule, sends inputs to PFC. We are currently performing detailed analysis of the molecular characteristics of key input areas to establish how specific cell-types provide input to the PFC circuitry. In summary, our comprehensive yet detailed circuit analysis provides a connectivity map reflecting the cellular and physiological underpinning of cognition. 1 Pollak Dorocic, I. *et al.* A whole-brain atlas of inputs to serotonergic neurons of the dorsal and median raphe nuclei. *Neuron* **83**, 663-678, doi:10.1016/j.neuron.2014.07.002 (2014).

Disclosures: Y. Xuan: None. **S. Ährlund-Richter:** None. **D. Fürth:** None. **K. Meletis:** None. **M. Carlén:** None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 638.10/DD56

Topic: G.03. Staining, Tracing, and Imaging Techniques

Title: Whole mouse brain fluorescence imaging at synaptic resolution

Authors: *X. HANQING, S. ZENG;
Huazhong Univ. of Sicience & Technol., Hubei, China

Abstract: Authors: H. Xiong[1,2], T. Yang[1,2], L. Su[1,2], A. Li[1,2], S. Jin[3], Z. Shang[1,2], Y. Jia[1,2], K. Huang[1,2], X. Lv[1,2], S. Li[1,2], Y. Li[1,2], N. Li[1,2], L. Liu[1,2], T. Xu[1,2], F. Xu[3,1], H. Gong [1,2], S. Zeng[1,2]*, Q. Luo[1,2]* **Affiliations:** [1]Britton Chance Center for Biomedical Photonics, Wuhan National Laboratory for Optoelectronics-Huazhong University of Science and Technology, Wuhan 430074, China [2]Key Laboratory of Biomedical Photonics of Ministry of Education, Department of Biomedical Engineering, Huazhong University of Science and Technology, Wuhan 430074, China [3]Wuhan Institute of Physics and Mathematics, Chinese Academy of Sciences, Wuhan, China *Corresponding author. E-mail: sqzeng@mail.hust.edu.cn and qluo@mail.hust.edu.cn.

Abstract: The complex anatomical structures of individual neurons and their synaptic connections form the signal transmission and processing pathway of the nervous system, and therefore are basis for understanding brain functions. However, existing imaging methods cannot cover the huge extension of neurons in mammalian brain with a resolution sufficient to identify connection sites (the pre- and postsynaptic structures). Here we proposed the chemical sectioning (CS) method that enables whole-mouse-brain imaging of genetically defined neuron subsets at synaptic resolution. For the first time, we show the successful reconstruction of individual neurons extending axonal projections throughout the brain, including all dendrites, centimeter-extended axonal main stems, terminal arborizations, intensive dendritic spines and axonal boutons, and putative synapses. Our method enables quantitative analysis of the morphology, projections, and connectivity of genetically defined neurons. We found that three typical projections (the corticospinal, corticostriatal and corticothalamic projections) can be covered by one layer-V pyramidal neuron.

Disclosures: **X. Hanqing:** None. **S. Zeng:** None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 638.11/DD57

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: HHMI

Title: High-speed volumetric imaging of neuronal network activity in awake behaving mice

Authors: *L. KONG[1], M. CUI[2];
[1]HHMI/Janelia Res. Campus, Ashburn, VA; [2]Howard Hughes Med. Inst., Ashburn, VA

Abstract: Neural computations rely on the spatiotemporal properties of the densely-interconnected neuronal network. To study the neuronal ensemble activity, several 3D optical imaging techniques have been proposed. But due to the motion artifacts, it is still challenging for high-speed imaging of neuronal network activity in awake behaving animals. Meanwhile, fast 3D imaging with behaving animals is highly desired to study behavior or task related neuron activity. We recently developed a high-speed volumetric imaging technique with high spatiotemporal resolution. Combining an optical phase-locked ultrasound lens and a conventional two-photon fluorescence microscope, we achieved a cross-sectional frame rate of ~1 KHz, which enables high-speed volumetric imaging of biological dynamics in deep tissue.

Here we apply this technique to fast 3D imaging of neuronal network activity in head-restrained awake behaving mice with high temporal and spatial resolution.

Disclosures: **L. Kong:** None. **M. Cui:** None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 638.12/DD58

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: FAPESP 14/21984-1

Title: Microglia 3D reconstruction with planar fluorescence microscopy and CLARITY histology

Authors: ***G. M. ARISI**, F. ZANINI;
Univ. Federal De Sao Paulo - UNIFESP, SAO PAULO, Brazil

Abstract: Introduction Microscopy and histological techniques greatly advanced our understanding of the fine cellular structure of nervous tissue. Nonetheless, the complex tridimensional organization of neurons, glial cells and vasculature is lost in sectioning the brain in order to analyze it under the microscope. Laborious and time-consuming methods are employed to reconstruct the 3D organization of cells. Objective and Methods Advanced histological techniques like CLARITY, that preserves the cellular protein structure *in situ* and renders the nervous tissue transparent to light by removing the cellular lipid layers, will allow studies encompassing large volumes of different brain regions. Combining this histology to Selective Plane Illumination Microscopy (SPIM), or planar (light-sheet) fluorescence microscopy, makes possible a laser scanning of different immune labeled proteins of interest in large cellular populations. FIJI software can perform morphological quantitative analysis on digital images. Results Ten female rats were perfused (IACUC/CEUA 6744240414) and after thermal polymerization the brains were positioned in a electrophoretic chamber for lipid removal at 37 ºC and 40 V for 4 days and in 37 ºC bath for more 4 days rendering the tissue transparent. Immunohistochemistry for Iba-1 (Wako, lot 019-19741) was performed in 1 mm blocks and visualized in laser microscopy. Microglial cells were visible in large areas of both cortex and hippocampus. FIJI was employed to cell count in different brain areas and analysis of morphometric parameters. Discussion Transparent blocks of nervous tissue allow study of large cell populations; this histological preparation saves time in 3D studies of complex structures.

Nonetheless a new kind of microscopy has to be developed to fully take advantage of CLARITY histology. A standard confocal laser scanning fluorescent microscope was employed to visualize the labeled cells while our lab implement the light-sheet microscope. In practical time frames is possible to map glial and neuronal cellular structures in the brain. Development of open platforms using common off-the-shelf parts will create local trained personnel able to build and maintain the OpenSPIM setups. CLARITY, OpenSPIM, and FIJI constitutes powerful tools for neuroscience research labs. Financial support FAPESP 14/21984-1

Disclosures: G.M. Arisi: None. **F. Zanini:** None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 638.13/DD59

Topic: G.03. Staining, Tracing, and Imaging Techniques

Title: See-through cortex: flattening technique improves clearing speed and imaging

Authors: *J. L. BALSOR[1], J. M. MATTINA[2], S. MOLOT-TOKER[1], K. M. MURPHY[2]; [1]McMaster Integrative Neurosci. Discovery and Study, [2]Psychology, Neurosci. & Behaviour, McMaster Univ., Hamilton, ON, Canada

Abstract: Innovative tissue clearing techniques make it easy to render the brain see-through and visualize its detailed neuroanatomy. For example, columnar and area specific features in the cortex are preserved so their full 3-D anatomy can be studied. But it can take several weeks to clear the entire brain and imaging that 3-D structure relies on expensive microscopes that are not widely available. We have taken a different approach to solve these problems for studying cortical neuroanatomy by combining unfolding and flattening of the cortex with a simple tissue clearing method -- passive clarity technique (PACT). To validate the approach we first asked if PACT clears the cortex uniformly. We perfused rats with PBS, removed the brain, resected the cortical hemispheres, and gently flattened them between glass slides. The cortex was fixed by placing it in 4% paraformaldehyde for 30 minutes, then removing the slides and leaving the cortex in fix for an additional 3-5 hours. The fixed cortex was then infused with a hydrogel monomer solution of 4% acrylamide in PBS for 2 days. The monomer-infused tissue was heated for 4 hours to polymerize the hydrogels. The cortex was cleared by transferring samples to an 8% SDS solution, and applying gentle agitation while maintaining a constant temperature of 37°C. The clearing process was monitored by imaging the cortex on a flatbed scanner every 4-8 hours and quantifying the optical density across the cortex. There was uniform clearing of the

cortex over 4 days and it became optically transparent following an exponential decay (y=0.16+1.16*exp(-x/10.14). Next, we determined if anatomical features in the cleared flat cortex could be imaged using readily available scanning and microscopy techniques. We labeled the see-through cortex with fluorescent stains and imaged at low magnification using a fluorescent scanner (LiCor Odyssey) and at higher magnification (10x) with a fluorescent microscope and a confocal microscope. These imaging techniques worked well for visualizing cortical anatomy over a range of magnifications. Our results show that combining PACT with unfolding and flattening of the cortex significantly accelerates the clearing process, and makes it easy to image cortical anatomy.

Disclosures: **J.L. Balsor:** None. **J.M. Mattina:** None. **S. Molot-Toker:** None. **K.M. Murphy:** None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 638.14/DD60

Topic: G.03. Staining, Tracing, and Imaging Techniques

Title: This is a brain-wide precision imaging method

Authors: *H. GONG, X. LI, A. LI, J. YUAN, Q. LUO;
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Abstract: Brain-wide Precision Imaging Method for type-specific circuits with cytoarchitectonic landmarks High-precision and highly accurate methods are necessary to study organisms with extremely complex structures, particularly when studying the brain. The study of neural circuits that distributed in the brain through neurites, i.e. axons and dendrites, is essential to understanding how the brain operates when healthy, injured or diseased. However, current knowledge about the intricate patterns of neural circuits is extremely sparse. For investigating these distributions, it would be ideal not only to be able to visualize neural circuits consisting of local and long-distance connections at single neuron resolution in a entire mouse brain but also achieve the neuron location information simultaneously. In fact, this kind of tracing requires continuously imaging the fine structures of neurites across the whole brain with one-micron voxel resolution. In this presentation, we introduce a fluorescence wide-field large-volume tomography (WVT) method. Combined with block sectioning, a fast and robust and high precision fluorescence imaging was achieved by a structured illumination microscopy. We also introduced a novel resin-embedding method optimized for fluorescent protein labelled mouse

brain to provide both adequate specimen hardness and fluorescence intensity. With these techniques, we acquired two colors whole brain datasets of an 8-week-old C57BL/6J mouse injected of the adeno-associated virus vector plasmid (AAV, expressing GFP) into the cingulate cortex (Cg) with voxel size of 0.32× 0.32 × 2 m^3 in 3 days. We could not only show a group of axonal projection pathways, but also discovered a new axonal long-distance projection from a neuron oriented in the Cg. With advanced labelling techniques, our method is believed to open an avenue to exploring both local and long-distance neural circuits and cell types that are related to brain functions and brain diseases down to the neurite level.

Disclosures: H. Gong: None. **X. Li:** None. **A. Li:** None. **J. Yuan:** None. **Q. Luo:** None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

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Program#/Poster#: 638.15/DD61

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: NHMRC Grant (APP1086643)

Australian Research Council Centre of Excellence for Integrative Brain Function (ARC Centre Grant CE140100007)

Title: Imaging the mouse spinal cord cyto- and chemoarchitecture with CLARITY

Authors: *G. SENGUL[1], H. LIANG[2], G. PAXINOS[2];
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Abstract: The organization of the mouse spinal cord, with ten Rexed laminae and thirteen spinal cord nuclei, has been shown in detail in our recent publication Atlas of the Spinal Cord of the Rat (Sengul, Tanaka, Watson, Paxinos, Academic Press Elsevier, 2013). Until recently, the only way to visualize the spinal cord in 3D was to do serial sections and reconstruct these. However, tissue sectioning and subsequent imaging of individual sections have various limitations. CLARITY is a new technique developed in the Deisseroth Lab at Stanford. The present study was designed to show organization and chemo-architecture of the mouse spinal cord in 3D using CLARITY, to reveal new details and be a guide for further cord studies using this technique. C57BL/6J mice were perfused with ice cold hydrogel solution, spinal cords cut into 2-3 mm segments and washed with clearing solution until optically transparent as described by Chung et al. (Nature Methods 10:508-513,2013) and imaged using a multiphoton microscope. Calbindin,

calretinin, parvalbumin, CGRP, ChAT, serotonin, glycine, GAD67, NOS and GABA immunostaining revealed details of the 3D organization and chemo-architecture. Neurons in different laminae were observed with their projections in 3D, e.g., expressing calbindin, calretinin, ChAT, CGRP, GABA, glutamate, glycine and NOS in lamina 1, calbindin, calretinin, ChAT, GABA, glutamate, glycine, NOS and parvalbumin in lamina 2, calbindin, calretinin, CGRP, GABA, glycine and NOS in lamina 4, CGRP, GABA, CGRP, glycine, NOS and parvalbumin in lamina 5-6, calbindin, calretinin, GABA, glycine, NOS, and parvalbumin in lamina 7, CGRP and ChAT in lamina 9, and calbindin, calretinin, CGRP, GABA, glycine, NOS and parvalbumin in lamina 10. With this study, the cyto- and chemo-architecture of the mouse spinal cord have been observed in 3D for the first time using CLARITY.

Disclosures: **G. Sengul:** None. **H. Liang:** None. **G. Paxinos:** None.

Poster

638. Whole-Brain Imaging and Atlasing I

Location: Hall A

Time: Tuesday, October 20, 2015, 1:00 PM - 5:00 PM

Program#/Poster#: 638.16/DD62

Topic: G.03. Staining, Tracing, and Imaging Techniques

Support: Howard Hughes Medical Institute

Title: A platform for brain-wide imaging and reconstruction of individual neurons

Authors: ***M. N. ECONOMO**[1], N. G. CLACK[1], L. D. LAVIS[1], C. R. GERFEN[2], K. SVOBODA[1], E. W. MYERS[3], J. CHANDRASHEKAR[1];
[1]HHMI/Janelia Res. Campus, Ashburn, VA; [2]Natl. Inst. of Mental Hlth., Bethesda, MD; [3]Max Planck Inst. of Mol. Cell Biol. and Genet., Dresden, Germany

Abstract: The structure of axonal arbors controls how signals from individual neurons are routed within the brain. However, the arbors of very few long-range projection neurons have been reconstructed in their entirety. In mammals, axons with diameters as small as 100 nm arborize in target regions dispersed over millimeters of tissue. For this reason, visualizing complete axonal arbors requires the determination of structure over length scales spanning many orders of magnitude. We describe a platform for high-resolution, three-dimensional fluorescence imaging of large, complete tissue volumes that enables the visualization and reconstruction of long-range axonal arbors. This platform relies on a high-speed two-photon microscope integrated with a tissue vibratome and a suite of computational tools for large-scale image data as well as novel methodology for optical clearing of brain tissue. We demonstrate the power of this

approach by reconstructing the axonal arbors of multiple individual motor cortex neurons spanning all cortical lamina within a single mouse brain.

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